ISSN 1443-850X

Bioshares

27 March 2015
Edition 593

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

Companies covered: Biogen, ACW, BNO, CGS, TIS

	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)	9.1%
Cumulative Gain	**392%**
Av. Annual gain (14 yrs)	**16.7%**

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

Blake Industry & Market Analysis Pty Ltd
ACN 085 334 292
PO Box 193
Richmond Vic 3121
AFS Licence
No. 258032

Enquiries for *Bioshares*
Ph: (03) 9326 5382
Fax: (03) 9329 3350
Email: info@bioshares.com.au

David Blake - Editor
Ph: (03) 9326 5382
Email: blake@bioshares.com.au
Mark Pachacz - Research Principal
Ph: 0403 850 425
Email: pachacz@bioshares.com.au

Individual Subscriptions (48 issues/year)
$440 (Inc.GST)
Edition Number 593 (27 March 2015)

Has Biogen Found A Disease Modifying Treatment For Alzheimer's Disease?

Has Biogen Idec, soon to be renamed Biogen, cracked the biggest nut in drug development, finding an effective treatment for Alzheimer's disease? This week the company released very encouraging data from a Phase Ib trial of aducanumab in 165 patients with prodromal and early stage disease. The results were encouraging enough that Biogen plans to move straight into a Phase III trial this year.

Aducanumab binds to aggregated beta-amyloid in the brain, both soluble oligomers and insoluble fibrils, according to the company. Biogen has achieved efficacy data that other companies had been unable to achieve using a similar approach. The compound is delivered monthly via an intravenous infusion.

What was impressive about the result was not only that it had been able show distinct advantages in cognition over placebo in a relatively small study, the effects were clinically meaningful, but also that the effect was strongly dose and time dependent. The cognition benefit was also statistically significant on one measure (MMSE score) at two different doses and statistically significant on another cognitive measure (CDR-sb) at the highest dose.

The trial was conducted over 54 weeks, with a read out also at 26 weeks. Doses were 1mg/kg, 3mg/kg, 6mg/kg and 10mg/kg. There was an almost linerr increase in plaque reduction in the brain with increasing dose at 26 weeks which continued to increase at 54 weeks.

One third of the patients recruited into the trial were confirmed with prodromal Alzheimer's disease and two thirds had early stage disease. The effect of the drug appears to be more pronounced in the second six months of treatment. Cognitive decline continued at all doses at six months, however at 12 months, the highest dose of 10mg/kg appears to have arrested cognitive decline showing an improvement in cognitive function at 12 months. This was not seen at the 3mg/kg dose at the 12 month readout and the 6mg/kg dose was not included in a presentation of the data this week at the Alzheimer's and Parkinson's diseases conference in Nice.

The upshot is that an ideal dose looks to be somewhere between 3-10mg/kg.

Cont'd over

– Biogen and Aducanumab cont'd

One Concern With Aducanumab

The only concern with this drug candidate is an adverse event listed as ARIA-E (Amyloid Related Imaging Abnormality Edema) or brain edema, which was also dose dependent. At the highest dose of 10mg/kg, the incidence of ARIA-E was 17%.

However, ARIA-E escalated in patients carrying the ApoE4 gene linked to Alzheimer's disease to 55% of patients at the high dose. At the 3mg/kg dose, the incidence was 9% and 5% respectively (that is 5% in patients carrying the ApoE4 gene) which is more manageable.

This data suggests that the one downside to this drug is its narrow therapeutic window.

The effect of ARIA-E was not shown to be dangerous. Patients who developed ARIA-E could either discontinue treatment (of which 46% did), pause treatment or move to a lower dose, or elect to stay on treatment.

In 78% of cases, the brain swelling was mild-moderate, generally resolving within four weeks. The concern is that in 65% of cases, there was no obvious symptoms of brain swelling. So this side effect will need to be monitored. Phase III trials with another anti-amyloid antibody bapineuzumab also displayed an edema side effect in patients.

Arguably, the occurrence of brain edema reflects the effectiveness of the treatment. Researchers involved with the trial believe these side effects are monitorable and manageable.

With 92% of cases observed in the first five weeks, and most symptoms resolving within four weeks, of interest will be the incidence of edema in longer term use of the drug candidate. An extension study is continuing, which will provide further valuable information on extended use, and cognitive benefit past 12 months.

In other outcomes of interest, only 3% of patients developed an antibody response to the drug.

Net Closing In On Elusive Alzheimer's Therapy

A number of important developments have occurred over the last five years that are bringing the elusive goal of finding a disease modifying Alzheimer's disease drug closer to market. The most significant of these has been the introduction of imaging agents into clinical trials that can definitively detect and show the presence of plaque build up in the brain.

The first of these was PiB (Pittsburgh compound B). Effectively taking the blindfolds off drug developers, biotech and pharmaceutical companies now not only know for certain which patients have Alzheimer's disease going to clinical trials, but also can visualize changes in the level of plaque in the brain in response to experimental drug treatments.

Previously the only way to 100% guarantee the existence of disease was through a brain autopsy following death. In the Phase III studies with bapineuzumab in Alzheimer's disease, 25% of patients actually did not have the disease.

Another important development have been the findings from failed Phase III and Phase II trials with anti-amyloid antibody therapies in Alzheimer's disease.

In two Phase III trials with bapineuzumab (Pfizer and Johnson & Johnson), the drug candidate did not reach its efficacy endpoint.

In two Phase III studies with solanezumab (from Eli Lilly), the primary endpoint of cognition benefit was also not reached. In two Phase II trials with crenezumab (Genentech), the endpoint of slowing cognitive decline was also not met.

However, what has been learnt from these trials is that anti-amyloid therapies need to be introduced at an earlier stage of disease. With solanezumab and crenezumab, dissection of the data did show efficacy benefit in patients with mild forms of the disease.

This is now where drug developers are moving with anti-amyloid therapies and the FDA appears to be lowering the bar for drug developers.

Cont'd over

Selected Phase III Clinical Studies Underway in Alzheimer's Disease

Company	Compound	Trial size	Indication	Trial start	Expected completion	Comments
Forum Pharmaceuticals	EVP-6124, potentiator of alpha-7 receptor	790, 6 months treatment	Mild-moderate Alzheimer's	Early 2014	2H 2016	Achieved stat sig results 6 month Phase II trial
Eli Lilly	Solanezumab, anti-amyloid antibody (against soluble AB only)	2100, 1.5 years weeks treatment	Mild Alzheimer's	Jul-13	Dec-16	Failed in mild-moderate disease
Merck	BACE inhibitor, MK-8932	1960, 1.5 years treatment	Mild-moderate Alzheimer's	Dec-12	Jul-17	84% drop over 7 days in AB42 levels in CSF
Merck	BACE inhibitor, MK-8931	1500, 2 years treatment	Prodromal	Nov-13	Mar-18	84% drop over 7 days in AB42 levels in CSF
AstraZeneca & Eli Lilly	BACE inhibitor, AZD3293	1551	Early Alzheimer's	Sep-14	May-19	Sig reduction in AB levels in CSF in Phase I
Eli Lilly	Solanezumab, anti-amyloid antibody (against soluble AB only)	1150, 3 years treatment	Prevention in at-risk patients with plaque build up	Feb-14	Apr-20	Failed in mild-moderate disease
Biogen	Aducanumab, anti-amyloid antibody (against soluble & insoluble AB)	n/a	Mild/prodromal	2015	n/a	Stat sig Phase Ib results (165 patients), edema side effect, narrow therapeutic window

– Biogen and Aducanumab cont'd

Noting the difficulty in measuring changes early on in functioning, measuring benefits in cognitive changes tied to changes in biomarkers may be adequate endpoints. Also, just slowing cognitive decline may be sufficient to gain approval from the regulator.

Other Approaches To Treating Alzheimer's Disease

As is the case in other diseases such as HIV and cancer, effective treatments in Alzheimer's disease are likely to incorporate a combination therapy approach, once those therapies become available.

Some researchers believe that it is a dysfunctioning tau protein in the body, which regulates axonal transport, that is the main culprit for cognitive decline and memory loss in Alzheimer's disease. The beta-amyloid protein is thought to interrupt with the signally pathway that regulates correct tau production in the brain.

Actinogen Medical (ACW: $0.08) this week moved into the second cohort of patients in a Phase I trial in healthy volunteers with its Alzheimer's disease drug candidate, Xanamem. Xanamem blocks production of the stress hormone cortisol in the hippocampus and frontal cortex, which is the part of the brain most affected by Alzheimer's disease. The company says there is increasing evidence that high cortisol levels and chronic stress affects memory and leads to amyloid plaque formation.

The company has completed the first eight patients at the lowest dose of 10mg. It is now moving on to a 25mg dose which will be followed by looking at the safety of a 35mg dose.

Forum Pharmaceuticals is running a Phase III Alzheimer's disease program with an alpha-7 nicotinic acetylcholine receptor potentiator (*partial agonist*). Last year, Bionomics (BNO: $0.465) licensed its alpha-7 nicotinic acetylcholine receptor *positive allosteric* modulator program to Merck which came with a US$20 million upfront payment, targeting cognitive dysfunction associated with Alzheimer's disease.

Merck is also following the BACE inhibitor approach (with MK-8931) for treating Alzheimer's disease and has the leading program in the BACE inhibitor space, followed by AstraZeneca, which has teamed up with Eli Lilly. BACE, or beta-secretase, is involved in the conversion of the amyloid precursor protein into beta amyloid.

In Merck's Phase Ib trial with its BACE inhibitor candidate in patients with mild-moderate disease, beta amyloid (AB40) levels in the cerebral spinal fluid were reduced by 84% in the highest dose in just seven days. There have been safety concerns over BACE inhibitors that has seen other groups end their programs.

Merck has successfully completed a three month safety study with MK-8931 in 200 patients, and is now continuing to enroll the remainder of the 1,960 patients in its Phase III study.

Implications for Cogstate

The implication of Biogen's results for cognition testing company Cogstate (CGS: $0.18) is that it can expect to see increased volume in clinical trial activity in the Alzheimer's disease space. Biogen is moving into a Phase III trial and will need to recruit patients with confirmed Alzheimer's disease, a service that Cogstate offers through its recently introduced Precision Recruitment product. It can be expected that Biogen will see competitors follow-up with similar programs.

Biogen's trial results support the role of the effect of plaque build up in the brain on diminishing cognition. This is likely to see additional funds invested into programs targeting beta-amyloid inhibition as a way of effectively treating Alzheimer's disease.

Bioshares recommendations:
Cogstate – **Speculative Buy Class A**
Bionomics – **Speculative Hold Class A**
Actinogen – **Speculative Buy Class A**

Bioshares

Tissue Therapies' European Quagmire

Tissue Therapies' shares (TIS: $0.115) slumped 38% this week after it received a request from the European Medicines Agency's (EMA) Committee for Medical Products for Human Use (CHMP) to provide it with more data regarding one of the components of its wound healing product, VitroGro ECM.

Tissue Therapies shares closed the week down 75% from a 12 month high of $0.46 recorded in September 2014, the month in which a response was anticipated from the EMA (the 180-day questions time point). When the 180-day questions did arrive on September 30, Tissue Therapies shares weakened to around the 30 cent level when it was learned that "definitive answers to a number of the 180-day questions will require further analytical data from the company's manufacturer.

A History of Delays in the Regulatory Process

Up to March 26, 2015, Tissue Therapies has seen 1,241 days, or 3 years and five months, elapse since the British Standards Institute (BSI) (a group designated as a Notified Body by the EMA) completed an audit of Tissue Therapies' quality systems in November, 2011. (See *chronology of events on the next page.)*

At that time, and even up until June 1, 2012, Tissue Therapies had been setting expectations of a European market entry in 2012, around mid year. However, in August 2012, the BSI, for reasons that are not clear to this day, decided to refer a question of classifying VitroGro under Device Rule 13, instead of as a Class III medical device under Device Rule 8, to the MHRA.

Thus in October 2013, the MHRA classified VitroGro as a Class III medical device under Rule 13, which meant that a new review encompassing manufacturing and quality data would be required, with the EMA's review clock running for 210 days. The overall time for the review would be in excess of that number because of Tissue Therapies' need to gather data for the submission and then later answer the EMA's questions from what is termed the 120 day time point (120 day questions) and the 180 day time point (180 day questions).

By September 2014, most of the 120 day questions were resolved.

In November, the EMA deferred acceptance of '180 day questions' response from Tissues Therapies to January, 2015.

By January 19, 2015, Tissue Therapies had supplied the balance of the answers for the 180 day questions to the BSI, ready for submission on February 26. However, the EMA then placed a month delay on the acceptance date to March 26, 2015.

The CHMP met from March 23-26, hearing oral submissions on March 25. The agenda for the meeting item 1.1 referred to EMEA/H/D/002831, which identifies an unnamed product with the descriptors 'insulin-like growth factor segment', 'hard to heal wounds, primarily venous leg ulcers', in reference to VitroGro ECM.

Tissue Therapies describes VitroGro as "an artificially created matrix protein designed from parts of proteins that normally provide attachment sites in healthy dermal matrix which guide cells during wound healing". So it appears the CHMP is seeking more information about the IGF-1 segment which is component of VitroGro (but not the vitronectin component).

The issue for investors stemming from this new request for information is that Tissue Therapies will have to wait until May 2015, when it meets with an EMA Scientific Advisory Working Party to "agree on studies that will satisfy the request for additional data."

One possibility is that VitroGro's CE Mark certification may not be received in 2015, even assuming the SAWP studies are relatively simple laboratory exercises which are completed in a timely manner in 2015, because of the slow pace of review by the EMA and the propensity for new questions to materialise.

Capital History - Tissue Therapies

Quarter	Type of Raising	Funds Raised ($M)
Q1 2015	Placement	$0.57
	Placement	$4.00
	Rights Issue	$3.70
Q4 2013	Placement	$3.00
	Rights Issue	$5.34
	Rights Issue	$1.70
Q1 2013	Placement	$8.70
Q3 2012	Placement	$1.00
Q2 2011	Rights Issue	$8.09
Q4 2009	Placement	$5.00
	SPP	$2.70
Q1 2009	Rights Issue	$1.87
Q3 2008	SPP	$0.74
	Placement	$0.37
Q3 2007	Placement	$2.02
Q1 2007	Rights Issue	$3.37
Q4 2005	Placement	$1.60
	SPP	$1.70
Q4 2004	Placement	$1.46
	Sub-total	**$56.9**
Q1 2004	IPO	$3.5
	Total	**$60.4**

Investment Considerations

Tissue Therapies has been badly damaged through and by the EMA's review process. Long term shareholders are likely to have lost faith with the company, which more than ten years after listing and around $60 million in equity funding, has failed to get VitroGro approved in Europe.

The company's recent $8.3 million capital raising means it can remain financial viable over the short-to-medium term while redirecting efforts to is US strategy for VitroGro. The challenge here is that, as it the company has stated, it will require between $15-$22 million to fund the US approval process for VitroGro, with an anticipated market launch in 2018 H2.

However, Tissue Therapies expects its US plans for VitroGro to be funded by international strategic investors.

Cont'd on page 5

European Regulatory History - VitroGro ECM

Date Announcement	DESPA*	DES1-11**	Event		Tissue Therapies Statement
1-Nov-11			British Standards Institute (BSI) an EU Notified Body, completes audit of quality systems of Tissue Therapies [Oct 28, 2011]	No non-conformances found	"The company is in a strong position for the start of key market sales in 2012."
1-Jun-12	213	213	Tissue Therapies asked to provide additional information to the BSI, which is assessing the company's CE Mark application for VitroGro		"We remain confident that the CE Mark will be granted in time for the planned start of sales at the end of June 2012."
8-Aug-12	68	281	BSI refers CE Mark application to the UK MHRA to determine whethere VitroGro should be classified under Device Rule 8 or Device Rule 13	BSI advises review to take 30 calendar days	The referral was made "despite the earlier written advice received by Tissue Therapies from BSI which stated that all examiner queries had been answered by the Company to the satisfaction of BSI and that a CE Mark certificate would be issues shortly."
30-Oct-12	83	364	MHRA classifies VitroGro ECM as a Medical Device Class 3 but under Device Rule 13; MHRA requires that a review of manufacturing and quality data is required which will take up to 210 days; the start date is to be advised	BSI has agreed earlier VitroGro's classification under Device Rule 8	"The company remains ready to start sales in the EU immediately CE Mark is granted."
18-Mar-13	139	503	TIS advises that an email on March 13 received from BSI that VitroGro should be regulated as a Medicine not as a Device	Tissue Therapies arranges independent review of BSI submission to EMA	"The assessment indicates that the submission to the EMA was poorly constructed and did not provide adequate information to the Medical Devices Group."
9-Sep-13	175	678	BSI submits VitroGro dossier to EMA on Sept 6, 2013		
26-Feb-14	170	848	HALF YEAR REPORT - Tissue said it had received questions from EMA, which will require information from the contract manufacturers (of VitroGro)	Assembling the data will take several months, which means the 'clock' will stop	"A favourable EMA opinion is now expected in the second half of 2014."
28-Jul-14	152	1000	Submitted response to EMA 120 day review questions	Lodging the response restarts the 120 day review 'clock'	"It was evident from the detailed analysis of EMA questions when these were received earlier in 2014 that the most definitive response would involve the development additional test methods for stability and release for sale of VitroGro EMD and that this would take a few months of work."
30-Sep-14	64	1064	EMA 180-day questions received from the BSI; most of the 120-day questions now classified as completely resolved		"Definitive answers to a number of the 180-day questions will require further analytical data from the Company's manufacturer."
4-Nov-14	35	1099	EMA defers submission of Tissue's 180 response to **26 January 2015** and EMA Review Committee assessment to **26 February 2015**	Tissue targets **19 Jan 2015** to submit its reponse to BSI	"This situation is frustrating but the company would appear to have certainty as to the timing for the last stage of the review for the approval of VitroGro ECM for sale in the UK and Europe."
21-Jan-15	78	1177	BSI informs TIS that the EMA has deferred acceptance of Tissue Therapies response to 180-day review questions by one month, new acceptance date is **26 Feb 2015,** new opinion date **26 March 2015**		
4-Feb-15	14	1191	HALF YEAR REPORT - Tissue said responses to all 180-day questions were provided by the Company to BSI on **19 January 2015**		
4-Feb-15	0	1191	ENTITLEMENT OFFER INFORMATION BOOKLET - Tissue said 180 day questions received and responses provided by BSI for submission on 26 Feb. 2015		"The 120 day response resulted in approximately 65% of all questions being classified by EMA as "completely resolved". The remaining questions have been addressed in the 180 day response..."
26-Mar-15	50	1241	During formal hearing CHMP (Committee for Medical Product for Human Use) states that it wants additional data on one of the components of VitroGro	Tissue Therapies to attend an EMA Scientific Working Party meeting in **May 2015** to agree on studies that will satisfy the request for additional data Tissue also withdraws application for a Scientific Opinion but not CE Mark application.	"The company is pleased that the EMA and the Notified Body are assisting the Company to achieve a definitive solution."

*DESPA Days elapsed since previous announcement; **DES 1-11 Days elapsed since 1-11-11

Bioshares Model Portfolio (27 March 2015)

Company	Price (current)	Price added to portfolio	Date added
Clinuvel Pharmaceuticals	$2.96	$4.15	December 14
Innate Immunotherapeutics	$0.185	$0.190	November 14
Circadian Technologies	$0.170	$0.160	November 14
Actinogen	$0.080	$0.050	September 14
LBT Innovations	$0.079	$0.130	July 14
pSivida	$5.100	$3.800	May 14
Impedimed	$0.845	$0.245	December 13
Analytica	$0.024	$0.025	December 13
IDT Australia	$0.205	$0.260	August 13
Viralytics	$0.430	$0.300	August 13
Tissue Therapies	$0.115	$0.255	March 2013
Somnomed	$2.70	$0.94	January 2011
Cogstate	$0.180	$0.13	November 2007

Portfolio Changes – 27 March 2015

IN:
No changes

OUT:
No changes

– Tissue Therapies cont'd

The company's decision to write off VitroGro inventory, worth $1.4 million, means that new stock must be manufactured, and which is likely to be consistent with any new requirements that stemmed from the EMA's review process. The company's recent capital raising includes a budget line item of $643,000 for manufacturing and stability testing, which may mean fresh funds will have to be found for more manufacturing at a later date.

Tissue Therapies is capitalised at $35 million. The company is in a weakened state because of a yet-to-be determined timeline for European certification for VitroGro and a regulatory environment which could impose more delays rather than the desired affirmative action.

The company could become a takeover target, with an acquirer seeking to take advantage of Tissue Therapies' weakened state and a period of uncertainty leading up to a possible affirmative action by the EMA

Such a tactic was attempted (unsuccessfully) by Retrophin, which made an unsolicited bid for Clinuvel Pharmaceuticals in July 2014, prior to Clinuvel's receipt of EMA approval for Scenesse in October, 2014.

We have revised our recommendation for Tissue Therapies from a Speculative Buy Class A to **Speculative Hold Class B,** in consideration of the EMA regulatory (May SAWP meeting) uncertainties ahead.

Bioshares recommendation: **Speculative Hold 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

Sell

Corporate Subscribers: Cogstate, Bionomics, Impedimed, LBT Innovations, Tissue Therapies, Viralytics, Phylogica, pSivida, Benitec BioPharma, Admedus, Calzada, Invion, Imugene, Analytica, Circadian Technologies, Reproductive Health Science, Regeneus, Innate Immunotherapeutics

Subscription Rates (inc. GST)

48 issues per year (electronic distribution): **$440**

For multiple email distributions within the same business cost centre, our pricing structure is as follows:	$700	2-3 email addresses
	$940	4-5 email addresses
	$1200	6-10 email addresses

To subscribe, post/fax this subscription form to:

Bioshares
PO Box 193 Richmond VIC 3121
Fax: +61 3 9329 3350

I enclose a cheque for **$** made payable to **Blake Industry & Market Analysis Pty Ltd**, or

Please charge my credit card **$** MasterCard ☐ Visa ☐

Card Number ☐☐☐☐ ☐☐☐☐ ☐☐☐☐ ☐☐☐☐

Signature _____ Expiry date _____

Subscriber details

Name _____

Organisation _____

Ph ( ) _____

Emails _____

_____

_____