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In this edition...
Pharmaxis will change its business model and cut costs by seeking funding from outside the company for its early stage programs. This is a blow for the original vision for the company established by former CEO Alan Robertson. Reality in the form of a CRL from the FDA bit. Until Pharmaxis meets with the FDA to discuss the next steps for Bronchitol in the US and it receives results from its Phase III trial in bronchiectasis patients, both expected this quarter, the stock will sit in a holding pattern. Starpharma's plans for Vivagel for the treatment of bacterial vaginosis have taken a further blow with a strong placebo effect occurring in its Phase II prevention trial. More work is needed to understand this placebo effect in this and in the earlier Phase III treatment trials.
Companies Covered: BLT, PXS, SOM, SPL

	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)	-6.0%
Cumulative Gain	**224%**
Av. annual gain (11 yrs)	**17.8%**

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Bioshares

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Pharmaxis Waits on Bronchiectasis Phase III Results and FDA to Set Future Direction

The key take-home message from the Pharmaxis (PXS: $0.35) quarterly conference call this week was that the company must wait until it receives the results of its recently completed Phase III trial of Bronchitol in bronchiectasis sufferers and to hold a meeting with the FDA to discuss the path forward for Bronchitol for cystic fibrosis in the US, following its receipt of a Complete Response Letter in March.

The FDA said that Bronchitol could not yet be approved and cited three issues. The first was the number of treatment-related drop-outs in CF301, which the pre-agreed primary statistical analysis could not account for. The second was the lack of statistical significance for the primary endpoint in the second of the two Phase III trials. The final concern was with haemoptysis (bleeding), especially in pediatric patients.

So far, the FDA has said a further clinical trial is required. However, new CEO Gary Phillips is concerned that this new trial will not simply be a replica of the two Phase III trials completed to date. His objective would be to see it 'designed to maximise the chance of a definitive result that can lead to approval'. Pharmaxis would like to commence this additional trial in the first half of 2014. Despite not knowing how long and how much it would cost, Phillips said that the last Phase III (CF302) trial could be used as a guide. It cost $12 million and took two years to fully complete.

The company could access the US$40 million funding facility from Novaquest that it secured in January to support this trial. The company has received US$20 million (AU$19.5 million) to date and has the option to access an additional US$20 million from January 2014. The facility permits Novaquest to receive payments from Bronchitol revenues in the US and Europe for a period of eight years in Europe and for seven years from Bronchitol's launch in the US.

Phase III Bronchiectasis (B305) Trial

Results of the Phase III Bronchiectasis (B305) trial are expected by the end of this quarter. This trial, in 485 patients, saw the last patient complete the study in March. Currently individual patient reports are being reviewed prior to the database being locked for analysis.

Bronchiectasis as a condition is an attractive market opportunity for Pharmaxis because no drugs exist to treat the problem and there are no other drugs in late stage development to clear mucous. And unlike cystic fibrosis, which is largely a Caucasian genetic disorder, bronchiectasis has large patients numbers in other parts of the world, for example, in Asia. Another important difference between bronchiectasis and cystic fibrosis is that the primary endpoint for the trial is to show a significant difference in the rates of graded pulmonary exacerbations in patients with bronchiectasis (treated with Bronchitol) compared to placebo.

Cont'd over

– Pharmaxis cont'd

Phillips said that 'a strong performance by bronchiectasis in achieving this primary endpoint across the total population and under lying sub-groups and supported by a number of secondary endpoints will allow Pharmaxis to file a label extension in Europe'. It would also support its discussions with the FDA regarding the filing of a marketing approval application.

Interestingly, Phillips believes that even if the Phase III result isn't that strong, the result can still add considerable value to the company because of the unmet need in bronchiectasis and because it will clarify any future work required.

Bronchitol – Progress in Europe and RoW

Since its approval 12 months ago in Europe, sales of Bronchitol in Europe have come largely from Germany. German sales in the March quarter were a little over $350,000, where sales have now been occurring for nine months. Germany has been the one major European country where pricing approvals have not been necessary to obtain.

Phillips recently attended a pre-launch of Bronchitol in France with leading cystic fibrosis physicians, an event at which he said the interest was high. French pricing agreement is expected this quarter.

Phillips said that France is different to other markets because the use of hypertonic saline (as a mucolytic) is quite low. What is also of potential value in France is that there are larger centres that treat CF patients. These centres have sufficient economies of scale to deliver ancillary services. Such offerings may be one of the reasons certain issues with patient adherence have arisen in Germany (see below).

Bronchitol has been launched in Austria on an individual patient reimbursement basis. Pricing approval was obtained recently in Denmark and pricing approvals are expected in Italy, the Netherlands, Sweden and Ireland later this year.

Phillips said that so far Pharmaxis has been successful in getting prices equal to or slightly lower than Roche's Pulmozyme, despite difficult economic conditions across Europe.

One shorter term revenue challenge according to Phillips is to concentrate on revenue opportunities in other parts of the world. Some Eastern Europe, Middle East and South American approvals can be achieved on basis of EU and Australian approvals. Another challenge is to accelerate reimbursement pricing in general.

In the UK, Bronchitol received a recommendation from NICE in October 2012. Bronchitol will be listed on the formularies of all CF centres covered by NICE recommendations. More recently, from the beginning of April, Bronchitol has been included on the UK's National Commissioning Guidelines thereby ensuring coverage for all clinics where CF patients are treated. There have been delays to gaining coverage in the UK because CF was the first orphan drug to move to a national funding approach, in contrast to current regional funding plans.

The German Experience

There are 7,500 people with cystic fibrosis in Germany of which half are adults, the segment for which Bronchitol is approved for use in Europe.

Germany is the only European country not restricted by the need to get a drug price approved. Pharmaxis has completed market research that suggests it can obtain a peak market penetration in Germany for Bronchitol of around 35-40%

Phillips said that Pharmaxis has obtained a 10% share of adults after nine months of sales, a position which he described as 'satisfactory. He noted that Pulmozyme has a share of 45% after 20 years in the market.

However, Phillips was blunt in stating that 'what is not satisfactory for me is patient adherence'. In other words some German patients are not using Bronchitol in the recommended manner, which is 400 mg twice a day. If patients used Bronchitol as prescribed, Phillips suggested sales would be 20% higher.

To address this problem, Pharmaxis will provide more patient support, particularly over the first six weeks of use, to compensate for the lack of resources in smaller German CF clinics.

The Pharmaxis plan will include providing support material to educate patients with the correct understanding of where Bronchitol fits with other treatment regimes and providing workshops for clinicians run by adherence specialists on techniques to improve adherence in CF patients.

Changes to Business Model

Pharmaxis announced in its quarterly call that it will makes changes to its business model. The company has a portfolio of early stage assets in development and it had been relying on revenues generated by Bronchitol in the US to fund the portfolio. With those revenues not on the table, Pharmaxis will be seeking to fund some or all of these early stage assets externally. The company is open to exploring a range of possibilities to achieve this objective.

Phillips said that the plan to reconfigure the Pharmaxis business model is 'well advanced' and for some parts, it has been initiated. He said that cash burn was likely to stay the same while restructuring costs are absorbed in the current quarter. However, cost savings should begin to appear following this quarter.

Summary

Pharmaxis is capitalised at $105 million. The company has $73 million in cash, as well as access to another $20 million from Novaquest.

An informed investment decision on Pharmaxis cannot be made until the bronchiectasis Phase III trial results appear and the company holds its post-CRL meeting with the FDA. The B305 results will be very important. This condition is completely different to CF and the adherence problem currently being observed in CF may be less of an issue with bronchiectasis patients where a dose-response is tied to exacerbations not lung function.

Bioshares recommendation: **Speculative Hold Class B**

Starpharma – Placebo Result Continues to Disrupt Outcome in BV Trials

Starpharma Holdings (SPL: $1.135) has released results from a Phase II trial which assessed its drug candidate Vivagel for the *prevention of recurrence* of bacterial vaginosis (BV). The trial result showed that the lower dose prevented recurrence in around 80% of patients. However, the problem for the company was that once again the placebo treatment outperformed expectations, delivering a result for Vivagel that was 'encouraging', but not great.

The AMSEL Criteria

One of the key measures in this trial is what's called the Amsel criteria, which includes a number of tests to assess the presence of BV. Using three of the four most important of these tests as judged by the FDA, the company showed that after 16 weeks of treatment, only 12% of women showed any recurrent BV in the 1% dose. This result did not achieve statistical significance, with a p-value of 0.0588 (the p-value needs to be less than 0.05 for the result to be deemed statistically significant).

The problem was, once again, that the placebo effect was not as expected. It was expected the placebo group (taking a placebo gel) would show a recurrence of BV in around 50%-60%. However, in this trial only 28% of women experienced recurring BV. So there is a benefit to 16% of women, where this result should have been a 40%-50% benefit.

Last November Starpharma reported the outcome from two Phase III results in the treatment of BV using Vivagel. Those trials showed that a statistically significant result was achieved at the time treatment was stopped, but not as measured by the primary endpoint, at two to three weeks after treatment had stopped. The company said that there appeared to be "several potentially confounding factors in the Phase III studies, including high placebo Clinical Cure rates at some sites". In fact once the patients stopped treatment with the placebo gel, they actually improved in the three weeks following.

That a statistically significant result was achieved when treatment stopped at seven days was expected to deliver a strong result in the Phase II prevention of recurrence trial reported this week.

Difference to Dose Ranging Study Results

What is also confounding is that such strong results were achieved, as expected, in the company's dose ranging Phase II study in the treatment of BV, reported in May 2011. In that trial involving 132 women, Vivagel was shown to achieve a clinical cure at two to three weeks after daily treatment for seven days had finished.

That result was highly statistically significant (p=0.006), with a cure achieved in 46% of women in the lower 1% dose, compared to only 12% cure in women receiving a placebo gel.

In the Phase III treatment trials reported in November last year, only 27% and 28% of women in the two trials reported a cure at two to three weeks after treatment finished, much lower that in the Phase II trial of 46%. But in what was a double whammy, the placebo result also improved from the 12% seen in the Phase II result to 21% and 28% success in the two Phase III studies.

Where to From Here?

Starpharma cited the results as encouraging and plans to move the program into Phase III trials. The costs will now need to be reassessed following this Phase II trial according to the company. One focus for the company will be to better understand why there has been such a positive effect in the placebo arms, in both this Phase II trial and the two Phase III treatment trials. In a published Phase III trial with the antibiotic metronidazole, recurrence in BV was seen in 60% of participants in the trial receiving placebo (compared to only a 28% recurrence in this Phase II trial).

In both Phase II studies (treatment and in the prevention of recurrence), the lower dose of Vivagel (1%) outperformed the higher dose (3%). The explanation for this is that the higher dose kills of too many of the good bacteria (lactobacilli) as well as the bad bacteria responsible for the symptoms of BV.

Funding?

Starpharma is currently sitting on cash of $33.2 million, giving the appearance of being well funded. While existing funds may be sufficient to fund the Phase III trials in the prevention of recurrence of BV, the company may need to top up its funds over the next 12 months.

Licencing?

Starpharma is engaged in discussions with 10 potential pharmaceutical companies regarding partnering Vivagel for BV applications. The company will not rule out doing a licensing deal before Phase III BV prevention trials commence, if a lucrative deal can be negotiated.

The company says that the appeal of this program is that it is potentially a billion dollar market and that its product will be a first-in-class therapy for which there are no existing therapies. The company is planning to move the program into a Phase III setting with or without a partner.

Although the Phase II results are encouraging, the placebo effect seen in this Phase II trial and the previous Phase III studies will need to be better understood to assure a more predictable result in subsequent pivotal studies.

Summary

The stock has received considerable buying support from one of its major shareholders, the M&G investment group in the UK, which has purchased around 3 million shares in Starpharma following the Phase II result, taking its stake to 12.04%.

Starpharma is capitalised at $322 million. Given that the Phase II result has delivered some ambiguous data, our expectation was that the stock should have weakened following this result. Launch of the company's condom microbicide product is now also overdue.

Bioshares recommendation: **Sell**

Bioshares

Bioshares Model Portfolio (12 April 2013)

Company	Price (current)	Price added to portfolio	Date added
Circadian Technologies	$0.275	$0.270	March 2013
Tissue Therapies	$0.155	$0.255	March 2013
Allied Healthcare	$0.029	$0.026	February 2013
Psivida	$2.16	$1.550	November 2012
Benitec	$0.013	$0.016	November 2012
Nanosonics	$0.455	$0.495	June 2012
QRxPharma	$1.12	$1.66	October 2011
Somnomed	$0.91	$0.94	January 2011
Cogstate	$0.370	$0.13	November 2007
Clinuvel Pharmaceuticals	$2.10	$6.60	September 2007
Universal Biosensors	$0.69	$1.23	June 2007

Portfolio Changes – 12 April 2013

IN:
No changes.

OUT:
No changes.

Somnomed Posts Soft Quarter Result

Unit sales for Somnomed (SOM: $0.91) declined in the March quarter by 4.1% over the December quarter. The company has two separate strategies to ensure continued strong growth in Europe and the US, its two major markets. The first is working as planned, and for the second, the US, the company has been busy restructuring and reinforcing its operations to accelerate sales.

In the March quarter, Somnomed sold 8,582 of its oral splints that stop snoring and correct sleep disordered breathing. This was down on the December quarter, during which the company sold 8,950 units. However, the result was still 8.6% higher than the previous March quarter in 2012. Total revenue for the March quarter was $4.33 million and revenue for the first nine months of this financial year was $13.3 million, up 25% over the previous corresponding period.

Local Distributors in Europe

In Europe, the company's strategy has been to acquire local distributors to allow it to expand and deepen penetration of its products.

In 2012, the company acquired distributors in Holland, France and Sweden. The Swedish business will allow the company to also expand into other Nordic countries, including, Norway, Finland, Iceland and Denmark.

Unit sales grew in Europe by an impressive 35% in the March quarter and we expect this region is approaching 40% of total sales. This confirms the company's European strategy, noting that this is a 35% increase in unit sales, not revenue (which would be higher, incorporating sales from the distributors, where unit sales do not necessarily increase by acquiring distributors to which it already sells devices).

Competitive Tension in the US

The US has become more competitive. Last year the company put in place a strategy to tackle this increasingly competitive market. In September last year it appointed Dr Kien Nguyen to head up its US operations.

In the same month the company appointed a VP of Managed Care, to coordinate reimbursement. In recent months Somnomed has also appointed a new VP of Finance and Administration, an Operations Manager, a VP of Sales and Marketing, a VP of Dental and a Chief Medical Officer, all based in the US.

Somnomed was aiming for the beefing up of its US team to translate into increased sales in this half. However, unit sales in this financial year will be 8%-10% lower than planned. The impact of the more aggressive path in the US, and in concentrating on not just the dental but also the medical channels (working with sleep care physicians) is not expected to make an impact now until the next financial year. The dental network has been well established in the US and is one of the company's core assets. There are currently around 2,500 dentists in the US trained to fit the Somnomed devices.

The timely investment Somnomed is making in the US market will help the company maintain its leading position globally in the mandibular advancement splint market for the treatment of sleep disorders. It is also an investment in long term, sustainable growth in the US market. Somnomed's European strategy has paid off quickly, delivering strong growth. The company has invested in the infrastructure in the US to return that business back to a high growth outcome. That investment will very likely pay off as well.

Somnomed is capitalised at $39 million with $2.6 million in cash at the end of the March quarter.

Bioshares recommendation: **Buy**

Bioshares

Buchi Joins Benitec Board

The former CEO of Cephalon, Kevin Buchi has joined the board of Benitec Biopharma (BLT: $0.013). This is a striking endorsement of the potential for Benitec's ddRNAi approach to gene silencing therapies.

Buchi is well known for the partnership set up between Cephalon (now Teva) and Mesoblast to access its's adult stem cell technology.

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

Corporate Subscribers: Pharmaxis, Starpharma Holdings, Cogstate, Bionomics, Biota Holdings, Impedimed, QRxPharma, LBT Innovations, Mesoblast, Tissue Therapies, Viralytics, Phosphagenics, Phylogica, Bluechiip, pSivida, Antisense Therapeutics, Benitec BioPharma, Allied Healthcare Group, Calzada, Bioniche, Atcor Medical, Invion, Circadian Technologies