

In this edition...

Mesoblast is the King of Timing. In September 2012, Sanofi handed back its licence to ex-USA (but not Japan) rights for Prochymal to Osiris, after US\$130 million has been paid to Osiris (through Genzyme which did the original deal). A mere eight months later Mesoblast signed a Letter of Intent with Osiris and has taken on Prochymal (excluding Japan for GVHD) plus other assets on very attractive terms. Calzada's wound and burn treatment technology is showing promise with positive results from two trials now available.

QRxPharma is ready to head back to the FDA with an updated NDA which will hopefully result in its combination opioid MoxDuo IR obtaining recognition for a superior safety profile.

Companies covered: CZD, MSB, QRX

	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 - Current)	58.3%
Cumulative Gain	464%
Av. annual gain (13 yrs)	19.8%

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Bioshares

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

Extract from Bioshares –

Calzada Makes Important Steps Forward in Changing Wound and Burns Treatment Paradigms

Calzada (CZD: \$0.08) has delivered two positive clinical trial results for its Novosorb technology this year.

The first was with its topical negative pressure (TNP) trial, and the second in repairing free flap donor sites. The first product provides an improved alternative over incumbent products.

The second potentially provides a more affordable and robust way to treat major wounds in the body.

A third, longer term application of the technology has the potential to provide a composite skin product that can cover 100% of the body. The technology is being championed by Adelaide plastic surgeon Professor John Greenwood.

TNP Trial Result

Last month Calzada reported a positive result in using the NovoSorb material in TNP dressing. In the 18 patient trial, it was shown that Novosorb achieved less fragmentation in the wound than existing products, and was easier to remove with less bleeding. That NovoSorb is biodegradable is also a benefit.

Calzada filed the product for approval in the US last month under a 510k pathway and if all goes well, the company expects approval in 2014 Q1. The company is currently in discussions with potential licensing partners.

Full Thickness Surgical Wounds Trial Result

This week Calzada released comprehensive results from a trial in 10 patients with full thickness surgical wounds. The trial showed that the NovoSorb product could very effectively be used as a dermal scaffold in what is called a Biodegradable Temporarily Matrix (BTM). In this trial, patients had a section of full thickness skin removed from one site that was used in reconstructive surgery in another part of the body.

The standard of care is to repair the donor site by using a thin skin graft from another part of the body. However because it is repairing a deep wound, a cavity in the skin remains that is only partially filled by the skin graft (see announcement 10 October 2013, page 7, top left photo - note that these are very graphic medical photos). This means that where the harvest site for the free flap procedure is the forearm, movements of tendons in the arm are visible after the area is treated.

The free flap donor site was filled with the polyurethane biodegradable NovoSorb polymer, which was later completed using a skin graft (21-49 days later). The outcome was a

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well treated wound that was flush with the surrounding skin, and with only a small amount (3.2%) of wound contraction (see announcement 10 October 2013, page 7, bottom right photo).

Substantially Better Appearance with NovoSorb BTM

Skin grafts contract depending on the thickness of the graft; thinner grafts will contract more. The NovoSorb BTM can be used to make thin skin grafts look like a thick graft according to Greenwood. The more contraction of a wound also affects functionality, with mobility restricted when there has been a lot of wound contraction, limiting mobility of limbs.

In discussion with *Bioshares*, Greenwood argued the NovoSorb product will 'massively improve appearance', looking similar to the collagen-based Integra product, which Greenwood said is very good but is also very expensive and prone to infection issues.

This Calzada trial result was a major advance for the technology because it shows that the NovoSorb polymer material can fill the wound site with a robust outcome that allows skin grafts to successfully complete treatment.

A detailed report from Greenwood was provided in the company announcement and the comments are worth highlighting.

In one patient, 'the skin graft took well, leaving him with an excellent result without visible underlying tendons.'

In another patient, 'The post-graft result is a wound flush with the surrounding skin surface, robust and durable. The underlying tendons move freely and without any evidence of graft tendering - unlike similar defects that have been primarily grafted over tendons.'

In a third patient, the treatment 'took well and has left her with a robust, well-contoured result, which was superior in contour and texture to the primary split skin graft.'

Greenwood said that the company has 'learnt loads' about applying this product to wound treatment from this trial. In some cases, there was fluid build-up under the BTM from fluid running down the tendons to the wound so there needs to be a drainage hole in the seal placed on the BTM to release the fluid build-up and prevent lifting of the BTM, which occurred in some cases.

One impressive feature of the NovoSorb BTM technology is that it could easily be salvaged and repaired when required, in cases such as infection, which occurred in some patients and was successfully treated. In one case 30% of the BTM from the centre of the dressing was successfully removed to treat an underlying infection. The BTM product subsequently integrated with the rest of the wound, which was a positive and surprising outcome.

For patients who were very ill and had difficulty healing all wounds, it was found that the BTM needed to be left on the wound sealed for longer before the skin graft was applied to complete the treatment.

Overall the BTM integration in the wound was 100% successful in nine from 10 patients, with the one patient (above) needing 30% of the BTM product removed to treat (successfully) infection.

Comparison with Integra

The NovoSorb BTM product is much more robust than the leading product on the market, called Integra. However Greenwood says because this is a collagen based product, if you don't get it exactly right then bacteria grows because it feeds off the collagen. With NovoSorb, because it is synthetic, bacteria can't feed off it according to Greenwood.

Calzada plans to file the NovoSorb BTM for approval in the US in Q1 2014 also under a 510k pathway as a dermal scaffold in surgical wound applications.

Burns Treatment

This technology wasn't designed for repairing free flap wounds, which it can repair quite easily says Greenwood, but for burns. The next clinical trial will be in the treatment of burn wounds. Greenwood says this is a much bigger challenge because of the size of the wounds that require treatment. Greenwood has received ethics approval to commence a clinical trial in Adelaide, which is expected to start before the end of the year.

A product for burns treatment will be used both in the first world, where the number of cases is falling because of better safety practices, and in the second and third worlds, where the number of cases is increasing.

In 2014 Q1, the company also expects to start a 10 patient burns trial in France.

Cultured Composite Skin: The Holy Grail of Burns Treatment, but a Much Longer Term Project

The urgency for the treatment of serious burn wounds is that the wound needs to be sealed to prevent infection and also water loss. Stopping the water loss also stops contraction of the wound. To treat burns wounds, a skin graft is taken from another part of the body. However for larger wound areas, finding sufficient donor sites is a problem, which is amplified where thick skin grafts need to replace deeper wounds.

A future application of this technology is the development of a cultured composite skin (CCS) product. Here a skin graft is taken and the skin cells are separated and grown in a bioreactor on the NovoSorb matrix. Greenwood said that a 10cm by 10cm graft treated in this way would be sufficient to produce enough composite skin sheets to cover the entire body within 21 days. Preclinical proof of principle studies in animal models have been achieved. The latest trial results in free flap surgery with Novosorb bring this application a step closer to a reality.

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Summary

Showing that the NovoSorb biodegradable material can be successfully incorporated into a wound for treatment is a major advance for Calzada. Greenwood suggested the technology is very close to entering a paradigm shift in the field of wound treatment.

With the results achieved this year, we expect this stock will start to receive increased attention from investors. And with the increasing attractiveness of the Polynovo assets, there is a strong argument that the company should focus on this technology rather than the Metabolic drug assets that have failed to deliver meaningful commercial value.

Bioshares recommendation: **Speculative Buy Class B**

Bioshares

How Bioshares Rates Stocks

For the purpose of valuation, Bioshares divides biotech stocks into two categories. The first group are stocks with existing positive cash flows or close to producing positive cash flows. The second group are stocks without near term positive cash flows, history of losses, or at early stages of commercialisation. In this second group, which are essentially speculative propositions, Bioshares grades them according to relative risk within that group, to better reflect the very large spread of risk within those stocks. For both groups, the rating “Take Profits” means that investors may re-weight their holding by selling between 25%-75% of a stock.

Group A

Stocks with existing positive cash flows or close to producing positive cash flows.

- Buy** CMP is 20% < Fair Value
 - Accumulate** CMP is 10% < Fair Value
 - Hold** Value = CMP
 - Lighten** CMP is 10% > Fair Value
 - Sell** CMP is 20% > Fair Value
- (CMP–Current Market Price)

Group B

Stocks without near term positive cash flows, history of losses, or at early stages commercialisation.

Speculative Buy – Class A

These stocks will have more than one technology, product or investment in development, with perhaps those same technologies offering multiple opportunities. These features, coupled to the presence of alliances, partnerships and scientific advisory boards, indicate the stock is relative less risky than other biotech stocks.

Speculative Buy – Class B

These stocks may have more than one product or opportunity, and may even be close to market. However, they are likely to be lacking in several key areas. For example, their cash position is weak, or management or board may need strengthening.

Speculative Buy – Class C

These stocks generally have one product in development and lack many external validation features.

Speculative Hold – Class A or B or C

Sell

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