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Companies covered: BNO, CUV, PAR, TIS, VLA

	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 - May '15)	23.0%
Year 15 (May '15 - current)	18.1%
Cumulative Gain	**554%**
Av. Annual gain (14 yrs)	**17.8%**

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Paradigm Biopharmaceuticals – Clinical Trial Underway in Bone Bruising

Paradigm Biopharmaceuticals (PAR: $0.33) listed last year, raising $8 million at $0.35 a share. The company is repurposing a proprietary formulation of an existing drug for two new indications, and is conducting proof-of-concept studies in those indications with a view to securing licensing deals, potentially as early as next year.

The drug, pentosan polysufate sodium (PPS), was developed in Germany in 1949 to treat blood clots. It has been in use for over 60 years and as such its safety profile has been firmly established. What Paradigm has discovered is two additional uses for the drug, the first to treat bone bruising (bone marrow edema), particularly from sports injuries, and secondly as an alternative treatment for allergic rhinitis (hay fever).

Paradigm's formulations of PPS are called Zilosul, an injectable product to treat bone bruising, and Rhinosul, an intranasal spray for allergic rhinitis.

Athletes who experience a severe joint injury, such as a ruptured ACL (Anterior Cruciate Ligament), are up to 10 times more likely to experience osteoarthritis in that joint as a result of bone marrow edema (BME) that can occur as part of the initial injury.

Mechanism of Action

In BME, Zilosul acts by suppressing cartilage degrading enzymes called MMPs, and acts as an anti-inflammatory agent and as a mild anticoagulant in micro-fractures in the bone.

Phase II trial underway in BME

Paradigm is currently conducting a Phase II study in Melbourne and Adelaide at sports injury clinics in 40 patients who have suffered an ACL injury. The first patient was treated in Melbourne last month at the Box Hill Sportsmed Biologic medical clinic (BHSB). That patient damaged their ACL during a netball match and was confirmed as having bone bruising of the knee.

The aim of the therapy is not just to prevent osteoarthritis, but to also reduce pain, resolve the bone marrow edema and protect the cartilage over the long term, according to Dr Ruben Branson from the BHSB clinic. Dr Branson has previously worked with players from the Collingwood Football Club and Melbourne Storm. However, this treatment is directed at amateur athletes as well.

Earlier this month the company opened its second clinical trial site, in Adelaide at the Southern Orthopedics clinic. Professor Jegan Krishnan, the Principal Investigator at the Adelaide trial site, is interested in exploring the therapy also because of the long term damage to the joint that can occur from bone bruising.

Cont'd over

"Some patients are waiting for surgery for six to 12 months and during this time inflammatory changes in the injured joint are building up and setting the scene for a long term disease process as a result of the BME lesions that may lead to post-traumatic osteoarthritis," according to Professor Krishnan.

Currently several patients in Melbourne and Sydney are being assessed at these sites. So far it has been mainly netball players that have been considered for the trial. Recruitment into the studies is expected to accelerate as the AFL football season gets underway. The company has also been active in building awareness of the study across local sports clinics. The company is aiming to recruit four patients a month and to complete the trial by years end.

Paradigm expects to get a first look at the trial data in 2016 Q3. The trial is due to complete in 2017 Q1. Pending positive results, Paradigm then intends to conduct a double-blinded, placebo controlled Phase II study in 2017 Q3, which will take between one to two years to complete.

Developing a repurposed drug has a number of advantages for biotech and pharmaceutical companies, including lower development costs to bring a drug to market (US$80 – US$170 million compared to US$1 billion for a new chemical entity), and a quicker path to market, taking 3 – 12 years compared to 10 – 17 years for a new chemical drug, with potentially only the one Phase III trial required by regulators. The success rate is also higher for repositioned drugs, at 25% compared to 10% for 'de-novo' drugs, according to Paradigm. Over 30% of new drugs approved are repurposed compounds.

Paradigm believes the potential market size for the BME indication is US$2.5 billion a year in the US for treating knee and ankle injuries alone. This is based on a drug treatment cost of US$1,750.

Results To Date

In an earlier exploratory study in five patients with BME, Paradigm showed that after 10 intramuscular injections of PPS over two and a half weeks, complete resolution of the bone bruising was achieved within four weeks.

In December last year Paradigm provided its drug candidate for the treatment of an elite athlete with BME under the TGA Special Access Scheme. Because the ACL injury was not recent, the patient was not eligible to enter the company's clinical trial.

That patient was not responding to current therapeutic and surgical treatments and required weekly drainage of fluid from the knee. After six intramuscular injections of Zilosul over three weeks, the patient's symptoms improved considerably; pain was reduced by 62% and joint function improved by 37%. Since treatment, the patient has also not required fluid to be drained from the joint.

Hay Fever Application (Allergic Rhinitis)

The second application of the PPS drug Paradigm is pursuing is in the treatment of hay fever (allergic rhinitis). In an animal model, Paradigm has shown that the drug acts both as an antihistamine and also as a corticosteroid by inhibiting inflammation. The reason for working in hay fever is that more than half the people with hay fever are not effectively treated with current medications, and it represents a US$11 billion market according to the company.

Paradigm has completed a high dose toxicology study in rodents (conducted by Charles River Laboratories) with its nasal spray version of the drug with no safety issues with the drug evident even at high doses. The company has also completed a preclinical study in a guinea pig model in a direct head-to-head comparison of Rhinosul with AstraZeneca's drug Rhinocort. Results from that study are expected to be published in July. The aim is to show comparable efficacy to Rhinocort but without the side effects.

A Phase Ia trial is expected to start in Q3 this year with the company's proprietary nasal spray formulation in 20 healthy volunteers. That will be an ascending, multiple dose, safety study. Three month stability data on the drug is expected to be available in June with the trial to start in July in Australia at a Phase I clinical trial site.

In December the company anticipates starting a Phase IIa placebo-controlled study in Sweden. That trial will be conducted in the hay fever off-season in a controlled room, whereby allergen is introduced to known hay fever sufferers. It is expected to be a very quick trial to conduct, with subjects recruited in advance and then challenged in a controlled environment.

Paradigm's CEO, Paul Rennie, believes that data from the guinea pig study, if positive, should start to generate interest from potential partners, with a deal possible after completion of the Phase IIa study in 2017.

Management

Paradigm's CEO Paul Rennie was previously COO at Mesoblast. Its board consists of the current and former chairmen of Bionomics (Graeme Kaufman and Chris Fullerton). It has also hired former Proteome Systems founder, Keith Williams, as VP of Business Development.

Partnering & Funding

At the end of the Phase II BME trial, and pending positive results in 2017 Q1, Paradigm may partner the program for further clinical development, which would bring non-equity funding into the company.

Paradigm may also have sufficient data from its hay fever study, both from a preclinical study comparing Rhinosul with AstraZeneca's drug Rhinocort, as well as data from a 40 patient study due to start in December this year in Sweden, with which to conduct a licensing deal with the Rhinosul product next year.

Paradigm had $5.2 million in cash at the end of last year. It has funding to complete its current Phase II BME study and conduct its hay fever studies. Early partnering income may remove the need to return to capital markets in the short-medium term. Paradigm is capitalised at $29 million.

Bioshares recommendation: **Speculative Buy Class B**

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