EDISON

Mesoblast

Initiation of coverage

Precursor to success

Pharma & biotech

Mesoblast is a leading mesenchymal stem development company, with two technology platforms (MPCs, MSCs) generating nine clinical candidates (four in Phase III, five in Phase II). Three alliances – Teva, JCR, Lonza – underpin the key late-stage programmes including Revascor (US$4bn peak sales potential). We value Mesoblast at A$2.6bn (A$8.07/share), which could rise to A$3.2bn (A$10.00/share) if upcoming catalysts are positive.

Year end	Revenue (A$m)	PBT* (A$m)	EPS* (c)	DPS (c)	P/E (x)	Yield (%)
06/12	27.8	38.6	(21.6)	0.0	N/A	N/A
06/13	24.2	(48.8)	(17.2)	0.0	N/A	N/A
06/14e	16.2	(64.8)	(20.4)	0.0	N/A	N/A
06/15e	16.2	(69.4)	(21.7)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding intangible amortisation, exceptional items and share-based payments.

Two stem cell platforms – generating a broad pipeline

Mesoblast is developing allogeneic 'off the shelf' stem cell products based on its proprietary mesenchymal precursor cell (MPC) and culture-expanded mesenchymal stem cell (MSC) technologies. Mesenchymal lineage stem cells show multiple anti-inflammatory and regenerative effects in human tissues, but limited immune response. MPCs and MSCs have broad intellectual property protection and can be purified, expanded and manufactured on a commercial scale.

Nine clinical programmes – multiple shots on goal

Mesoblast's multi-indication pipeline is targeting chronic diseases affecting large populations. Indications with positive Phase II clinical data include congestive heart failure (Revascor), spinal fusion (NeoFuse), intervertebral disc repair, Crohn's disease (CD), graft versus host disease (GvHD) and bone marrow transplantation (BMT). Revascor has blockbuster potential (peak sales US$4.0bn) if the planned pivotal trial confirms the Phase II reductions in hospitalisations and cardiac deaths.

Three strategic partnerships (to date), more likely

Major alliances – Teva Pharma, Lonza Group, JCR Pharma – reduce execution risk for Mesoblast's late-stage pipeline. The US$1.7bn alliance with Teva underwrites the development and commercialisation of its CVS (Revascor, acute myocardial infarction) and BMT programmes. JCR expands Mesoblast's reach to Japan with a partnership on GvHD. Lonza will ensure efficient and cost-effective manufacturing of MPC-based products. We see potential for further deals on the spinal franchise.

Valuation: rNPV of A$2.6bn (A$8.07 per share)

We value Mesoblast at A$2.6bn, or A$8.07 per share, based on a risk-adjusted net present value (rNPV) analysis. Our base-case rNPV represents c 30% upside to the current market capitalisation of A$2.0bn. Initiation of the Revascor Phase III trial (Q413), positive final Phase II data in disc repair (Q413) and start of the Phase III trial in spinal fusion (H114) would increase our rNPV to A$3.2bn or A$10.00/share.

26 November 2013

Price	**A$6.30**
Market cap	**A$1,999m**
	US$0.92/A$
Net cash (A$m) as at 30 September 2013	292
Shares in issue	317.4m
Free float	60%
Code	MSB
Primary exchange	ASX
Secondary exchange	OTCMKTS

Share price performance

%	1m	3m	12m
Abs	2.2	7.1	14.4
Rel (local)	3.0	2.5	(5.1)
52-week high/low	A$7.49	A$5.14	

Business description

Mesoblast is developing adult stem cell therapies based on its proprietary MPC and culture-expanded MSC platforms. It has six late-stage clinical trials across four areas: immunologic/inflammatory (Phase III), spine disease (Phase II), cardiovascular (Phase III ready) and cancer (Phase III). The CVS franchise, which is partnered with Teva, could enter Phase III for heart failure in Q413. Worldwide manufacturing of MPCs will be provided by Lonza.

Next events

Start of Revascor Phase III trial in CHF	Q413
Final Phase II results in disc repair	Q413
Results of Phase II trial for MPCs in type 2 diabetes	Q413
Update on Phase II trial of MPCs in AMI	2014

Analysts

Dr Mike Aitkenhead	+44 (0)20 3077 5736
Chris Kallos	+61 (0)2 9258 1160
Robin Davison	+44 (0)20 3077 5737

healthcare@edisongroup.com

Edison profile page

Investment summary

Company description: Leader in regenerative medicine

Mesoblast is an Australian-headquartered biotechnology company focused on adult stem therapies. The company's pipeline is based on its proprietary MPC and culture-expanded MSC technologies. Mesoblast had its origins in a collaboration between South Australia's Hanson Institute (which identified methods to extract MPCs) and Angioblast (founded by Professor Silviu Itescu) in 2002. Mesoblast was established in July 2004 (focused on orthopaedic indications for MPCs) and listed on the ASX in December 2004. It took a 33% stake in Angioblast (focused on CVS indications for MPCs), and acquired the remaining 67% in December 2010. Mesoblast has raised A$379m since its IPO. It had 76 employees – in Melbourne (20), New York (54) and Singapore (2) – as of June 2013.

In October 2013, Mesoblast acquired Osiris Therapeutics' culture-expanded MSC business for up to US$100m plus earnouts. It will pay an initial consideration of US$50m, potential clinical and regulatory milestones of US$50m, plus an earnout on future product sales (capped at 10%). In return, Mesoblast gained a platform (MSC) complementary to its (MPC) technology, a conditionally approved product (Prochymal) for acute graft versus host disease (aGvHD), two Phase III programmes (aGvHD and Crohn's disease) and a Japanese partner in JCR Pharmaceuticals.

Valuation: Risk-adjusted NPV valuation of A$2.6bn

We value Mesoblast at A$2.6bn (A$8.07/share) based on a risk-adjusted net present value (rNPV) analysis. This includes projected end-FY14 cash of A$211m. Our base-case rNPV represents c 30% upside to Mesoblast's current market capitalisation of A$2.0bn (A$6.30/share). Initiation of the Revascor Phase III trial (Q413), positive final Phase II data in disc repair (Q413) and start of the Phase III trial in spinal fusion (H114) would increase our rNPV to A$3.2bn or A$10.00/share.

Financials: Funded through major value inflection points

Mesoblast is a development-stage biotech company that should generate its first meaningful product revenues from FY16 onwards. It is well capitalised (cash of A$315m at end-FY13) following a c A$170m equity raise and has three (out of nine) ongoing Phase II/III programmes funded by partner Teva. Operating cash outflow (excluding interest income and tax) was c A$68m in FY13. Over the next two to three years, we expect the cash burn rate to increase (A$80-85m) as Mesoblast invests in clinical studies (potentially five Phase III trials ongoing by end-FY14) and in commercial-scale manufacturing processes for MPC and MSC. In the absence of additional financing and/or partnerships, we estimate that Mesoblast's cash runway extends into late FY17.

Sensitivities: Confirmatory Phase III data awaited

Mesoblast is subject to the risks typically associated with biotech company drug development, including the possibility of unfavourable outcomes in clinical trials and regulatory reviews, success of competitors, and commercial decisions by partners. The key stock specific sensitivities include:

1. Teva alliance – this underpins the development and commercialisation of three major clinical programmes (CHF, AMI, BMT). While Teva appears committed to funding the Revascor Phase III trial, we have limited insight into Teva's future strategic priorities (both R&D and commercial).
2. Final Phase II results in disc repair (Q413) – while positive interim results may be indicative, they are not conclusive of the final trial result.
3. Initial Phase II data in diabetes (Q413) – while this is primarily a safety trial, lack of efficacy signals could be perceived as having negative read across to other IV indications (RA, DN).
4. Phase II trial in AMI – initiation of this trial was not directly supported by prior clinical data, which adds an element of risk.

Company description: Precursor to success

Mesoblast is testing its MPC-based and MSC-based (Prochymal) products in a broad range of indications (Exhibit 1), which are based on supportive clinical and/or preclinical data. Partner Teva has received FDA clearance to commence a 1,700-patient Phase III study of the key MPC programme, Revascor, in patients with congestive heart failure (CHF). The pivotal CHF trial, which is being funded by Teva, is expected to start in Q413. A positive readout for the Phase II study in AMI (potentially 2015) could see the second cardiac indication for MPCs progress into pivotal development. Separately, Mesoblast's spine disease programmes have delivered positive final results (spinal fusion) or interim data (disc repair) in Phase II trials. Pending final disc repair data (Q413), the company plans to initiate at least one Phase III trial in spine disease (fusion or disc) in 2014. The Prochymal programmes will also progress over the next 12 months, with completion of recruitment into the Phase III trial for CD (H214), a Japanese regulatory filing for aGvHD by JCR Pharma (by end-Q114), and clarity on the US and European regulatory pathway for aGvHD (2014).

Exhibit 1: Mesoblast's clinical-stage pipeline

Platform (product), partner	Indications	Dose (delivery)	Status	Next milestones
Cardiovascular				
MPCs (Revascor), Teva	Congestive heart failure (CHF)	150m MPCs (Transendocardial injection)	1,700-pt Phase III study protocol cleared by FDA	Q413: start US enrolment, H214: start EU enrolment
MPCs, Teva	Acute myocardial infarction (AMI)	12.5m or 25m MPCs (intracoronary infusion)	225-pt Phase II study ongoing	2014: update on study 2015: potential headline data
Spine disease				
MPCs (NeoFuse)	Lumbar spinal fusion	25m or 75m MPCs (implanted into intervertebral disc space)	24-patient Phase II completed	H114: potential start of Phase III trial
MPCs	Lumbar intervertebral disc repair	6m or 18m MPCs (Intradiscal injection)	100-patient Phase II ongoing	Q413: final 12-month results, H114: potential Phase III start
Immunologic/Inflammatory				
MSCs (Prochymal)	Moderate-to-severe Crohn's disease (CD)	600m or 1,200m MSCs (intravenous infusion)	330-pt Phase III study ongoing	H214: complete Phase III recruitment
MPCs	Type 2 diabetes and diabetic nephropathy (DN)	Diabetes trial: 0.3m, 1m, or 2m MPC/kg (intravenous infusion) DN trial: 150m or 300m MPCS (intravenous injection)	Diabetes trial: 60-pt Phase I/II study ongoing DN trial: 30-pt Phase II study ongoing	Q413: headline results from diabetes study Q314 : Q314: headline results from DN study
MPCs	Biologic refractory rheumatoid arthritis	Xm MPCs (intravenous injection)	48-pt Phase I/II study	H115: headline results
Oncology				
MSCs (Prochymal), JCR Pharma - Japan	Steroid-refractory acute graft versus host disease (aGvHD)	2 x 10^6 MSCs/kg twice weekly for 4 weeks (intravenous infusion)	Canadian conditional approval. Expanded Access Treatment in US. 190-pt Phase III aGvHD study completed, 240-pt Phase III steroid-refractory aGvHD study completed.	Q114: Japanese filing by JCR H114: regulatory discussions (FDA, EMA) regarding potential filings
MPCs, Teva	Bone marrow transplantation (BMT)	One MPC expanded cord unit (intravenous infusion)	240-pt Phase III study ongoing	H217/H118: headline results

Source: Mesoblast, Edison Investment Research

Mesenchymal lineage cells – utility in various diseases

Stem cell research and the potential translational application of adult stem cells has advanced significantly in recent years. Numerous clinical studies have been conducted to investigate the efficacy of various types of stem cells to treat a range of indications, such as immune disorders, neurodegenerative and cardiovascular disease, bone and cartilage repair, and diabetes.

The development of mesenchymal stem cells (MSCs), multipotent stromal cells that can differentiate into a variety of cell types, has been the most advanced (and successful) so far. Prochymal was the world's first approved stem cell therapeutic, granted conditional approval in Canada and New Zealand to treat children with acute GvHD. Prochymal is also available in the US under an Expanded Access Program to treat acute GvHD in children and adults.

Focused on allogeneic 'off the shelf' MPC and MSC products

Mesoblast is developing allogeneic 'off the shelf' stem cell products based on its proprietary mesenchymal precursor cell (MPC) and culture-expanded mesenchymal stem cell (MSC) technologies. Mesenchymal lineage stem cells show multiple anti-inflammatory and regenerative effects in human tissues, but a limited immune response. MPCs and MSCs have broad intellectual property protection and can be purified, expanded and manufactured on a commercial scale. MPCs are believed to be the precursors of all MSCs in adults. MPCs are harvested from the bone marrow of young, healthy, unrelated donors using a proprietary technique to identify and isolate the cells. This technique is based on binding of monoclonal antibodies to specific markers (Stro-1/Stro-3) on the surface of MPCs and using magnetic-activated cell sorting (MACS) to remove the cells. The end result is a highly purified, homogeneous population of MPCs that can be expanded in culture in a well-controlled and large-scale manner.

Mesoblast's MPC therapy for heart failure (Revascor) is the primary driver of our valuation, so it is worth considering the potential mechanisms of MPCs in cardiac disease. Following injury to the heart muscle (ie myocardial infarction), the human heart is unable to replace the damaged tissue and a scar forms. Stem-cell based therapies for cardiac repair have shown promise in preclinical trials, due to their ability to augment endogenous repair or (potentially) regenerate damaged muscle cells (cardiomyocytes).[1] The dominant effect is likely to be through paracrine mechanisms – transplanted cells release soluble factors that promote cardiac repair and regeneration.[2] Paracrine signalling is particularly relevant to mesenchymal lineage cells, which promote angiogenesis (new blood vessel formation), prevent apoptosis (cell death), modulate immune responses, recruit stem cells and facilitate beneficial remodelling.[3] MPCs have shown efficacy in animal models of ischaemic and non-ischaemic heart disease, with evidence of cardiac repair and revascularisation, prevention of adverse remodelling and improved cardiac function.[4,5]

First strategic partnership – Teva alliance

Mesoblast's strategic alliance with Teva is a central component of its investment case, as it reduces execution risk for MPC product candidates in key therapy areas cardiovascular (CHF, AMI) and oncology (BMT indication). The original partnership was signed in December 2010 with Cephalon (a US biotech), which was acquired by Teva in May 2011. Exhibit 2 summarises the key deal terms.

Exhibit 2: Terms of Teva alliance

Development and commercialisation rights	Teva holds exclusive rights to selected cardiovascular (CHF, AMI), cancer (BMT) and neurologic indications. Teva is responsible for funding all late-stage development (Phase IIb, Phase III) and subsequent commercialisation.
Manufacturing rights	Mesoblast has retained all manufacturing rights and negotiated a transfer price that is based on a percentage (we assume 40%) of Teva's net in-market sales. This transfer pricing arrangement allows Mesoblast to retain a significant share of product economics.
Upfront and milestones	Mesoblast received an upfront payment of US$130m from Cephalon, which is being amortised over seven years. It is also eligible for up to US$1.7bn in milestone payments, which are triggered by regulatory approvals for each product/indication in major territories (ie Revascor approval for CHF in US and EU triggers estimated payments of US$150m and US$100m, respectively).
Equity stake	Cephalon acquired a 20% stake in Mesoblast for A$243m at A$4.35 per share (a 45% premium). Teva's current 17.6% stake is worth approximately A$350m.

Source: Mesoblast, Edison Investment Research

Teva's lack of cardiovascular franchise and core R&D focus on respiratory and neurology may raise questions about its commitment to the Mesoblast alliance. However, Teva has publically committed to fund the Revascor Phase III study and, most recently, submitted the IND filing to undertake the pivotal trial. With Teva's commitment to long-term commercialisation less clear, and noting its large equity stake in Mesoblast, there is a possibility it may look to monetise commercial rights prior to launch – potential triggers could be results of the interim analyses in the Revascor pivotal trial.

1 Levit et al, J Am Heart Assoc 2013; 2:e0000367).
2 Gnecchi et al, Circ Res 2008;103: 1204-1219.
3 Berry et al, Am J Physiol Heart Circ Physiol 2006;290:H2196-H2203.
4 Cheng et al, Cell Transplantation 2012.
5 Houtgraaf et al, Circ Res 2013; 8 May.

Second strategic partnership – Lonza manufacturing agreement

A prerequisite of the potential commercial success of MPC-based products will be Mesoblast's ability to manufacture them cost-effectively on a large scale. In September 2011, Mesoblast formed a strategic alliance with Lonza Group, a leading biologics contract manufacturer, to supply MPC products for clinical trials and long-term commercial requirements globally. An additional aim of the alliance is to reduce long-term COGS through exclusive access to Lonza's Singapore manufacturing facility for allogenic cells. This partnership helps Mesoblast manage its execution risk and, moreover, alleviates the need for Mesoblast to build its own manufacturing capability.

Under the terms of the agreement, Mesoblast has the option to require Lonza to construct a purpose-built manufacturing facility exclusively for the company. In return, Mesoblast will purchase agreed quantities of market products from the facility. Mesoblast can also buy out this facility at a pre-agreed purchase price two years after the facility receives regulatory approval. In February 2013, the FDA approved Lonza's manufacturing process to supply MPC products (ie Revascor) for US Phase III trials – under Investigational New Drug (IND) protocols – from both its Singapore and US facilities. This followed the successful transfer of the MPC manufacturing process to the Singapore facility, which will manufacture the product for pivotal trials. Stockpiles of product to FDA specification are currently adequate for the next 12 months of Phase III trials.

Third strategic partnership – JCR Pharma (Japan)

The Osiris deal expands Mesoblast's reach to Japan through an established collaboration with JCR Pharmaceuticals. Under the deal terms, JCR has exclusive Japanese rights to manufacture, develop and market Prochymal (also known as JR-031) for steroid-refractory aGvHD. The annual number of hematopoietic stem cell transplants (HSCTS) in Japan is c 3,500, of which a substantial proportion are likely to be autologous HSCTS at risk of subsequent aGvHD. JCR will bear all costs of bringing Prochymal to market. Mesoblast is entitled to (undisclosed) milestones on regulatory filing and approval, milestones on achievement of pre-determined net sales levels, plus future royalties. In October 2013, JCR announced that it would file for Japanese approval under the existing regulatory pathway by March 2014. We currently exclude Japanese Prochymal and MSC-based product sales from our model; however, the Japanese government has enacted a Bill to fast-track regulatory approval for stem cell therapies, which could create opportunities for conditional approval of Mesoblast's MSC and MPC products on relatively limited (ie Phase II) clinical data.

Intellectual property – broad portfolio covers MPCs and MSCs

Mesoblast's acquisition of Osiris broadens and complements its IP portfolio for mesenchymal lineage cells. It now has 61 patent families (26 MPC, 35 MSC) that provide long-term commercial protection for its product candidates in major territories. Key MPC composition-of-matter (COM) and use patents are granted in the US (expire 2029), Japan (2025), Europe (2024) and China (2025). Patents covering culture-expanded MSCs run through to 2025, with potential extension to 2031.

Exhibit 3: Intellectual property rights for MPCs in key territories

Territory	Expiry	Details
US	2029	Composition of matter (COM) patent (8,367,405) covering its current products. Patent extends by more than seven years the commercial rights already conferred by previous US COM patents.
	2025	Two COM patents (7,052,907; 7,947,266) that give Mesoblast exclusive ownership over MPCs dervied from a variety of sources including dental pulp ad adipose tissue, in addition to bone marrow.
		Patent (7,670, 628) that provides Mesoblast with rights to commercialise bone tissue generating products using MPCs.
		Patent (7,399,632) provides protection for Mesoblast's methods of purifying, isolating and enriching MPCs.
	2019	COM patent (7,122,178) that provides Mesoblast with exclusive rights to commercialise MPCs.
EU	2024	Patent (EP 1432991) covers identification and isolation of somatic cells and uses thereof
Japan	2025	COM patent (5265190) provides Mesoblast with exclusive commercial rights in Japan to all compositions-of-matter and uses.
China	2025	COM patents provide Mesoblast with exclusive MPC product commercial rights and protection through to 2025.

Source: Mesoblast, Edison Investment Research

Revascor for congestive heart failure

Exhibit 4: Summary – Revascor for CHF	
Rationale	Injecting MPCs into damaged heart muscle (left ventricle) may improve heart muscle function and clinical outcomes.
Dose/administration	Single dose of 150m MPCs administered by transendocardial injection (direct injection into left ventricle of heart via NOGA catheter)
Clinical data	60-patient Phase II trial showed improved clinical outcomes (reduced death/hospitalisation), heart function (LV remodelling) and functional exercise capacity.
Next news	Start of Phase III trial (Q413), following FDA clearance of study protocol (October 2013).
Forecasts	Approval and launch in FY19; peak in-market sales of US$4.0bn (A$4.4bn)

Source: Edison Investment Research

Disease overview – high prevalence and poor prognosis

Congestive heart failure (CHF) is a common condition that, despite treatment advances, is still associated with significant morbidity and mortality. Heart failure occurs when the failing heart cannot pump enough blood and oxygen to support other organs. CHF affects 1-2% of adults in developed countries, with prevalence rising to >10% in those over 70 years. While progress has been made in treatment, there is high overall annual mortality (5-20%), particularly in patients with severe (NYHA class IV[6]) symptoms. About half of CHF patients die within five years of diagnosis.

CHF is divided into systolic and diastolic heart failure: in systolic CHF the ability of the heart to contract is reduced, whereas diastolic CHF shows impaired cardiac relaxation and abnormal ventricular filing. The most common cause of CHF is reduced contraction of the left ventricle, or LV systolic dysfunction (LVEF<40%[7]), which accounts for 60% of patients. Systolic CHF usually results from coronary artery disease (myocardial infarction, chronic ischaemia); other causes include idiopathic cardiomyopathy, valvular heart disease, hypertension and toxin-induced (ie alcohol).

Current 'state-of-the-art' treatment for advanced systolic heart failure includes a combination of medical and device therapy. Renin-angiotensin-aldosterone (RAAS) blockers (along with beta blockers) are the key pharmacological therapies, as they improve mortality, heart function, heart failure symptoms and exercise tolerance, as well as reduce hospitalisations for decompensated heart failure. Devices are increasingly used in mild-to-severe (NYHA II-IV) CHF. Implantable cardioverter-defibrillators (ICDs) decrease mortality, and the addition of cardiac resynchronisation therapy (CRT) to optimal medical therapy improves symptoms and mortality.

While outcomes of CHF patients have improved with RAAS blockers, as well as more prevalent use of ICD and CRT, the overall prognosis of CHF patients remains poor. A review of Clinical trials in NYHA Class II-III patients on maximal medical therapy suggests one-year mortality of c 10-15%. In the RAFT trial, mild-to-moderate CHF patients had a four-year cardiac death rate of c 15-20% despite being on maximal medical and device (ICD + CRT) therapy.[8]

Market opportunity – 1.8 million addressable patients in the US

Revascor is targeting CHF patients with systolic dysfunction (LVEF≤40%) and mild-to-moderate symptoms (NYHA class II or III). The American Heart Association (AHA) estimates that 5.1 million Americans over the age of 20 have CHF, with c 670k new cases diagnosed every year; moreover, it projects a 25% increase in prevalence to c 6.4m by 2030. Approximately 60% of American patients (three million) have systolic heart failure, of which 60% (1.8 million) are classified as NYHA II to III). Based on these prevalence figures, we estimate the addressable market for Revascor at 1.8 million, or c 36% of the total CHF population. In the EU, the prevalence and incidence figures for

6 New York Heart Association (NYHA) classification assesses the severity of functional limitations and correlates fairly well with prognosis. NYHA classification (and % of patients at each stage): I – asymptomatic: no symptom limitation with ordinary activity (35%), II – mild: ordinary activity somewhat limited by dyspnoea (35%), III – moderate: exercise limited by dyspnoea with moderate workload (25%), IV – severe: dyspnoea at rest or with limited exertion (5%).

7 LEVF is the percentage of blood that is pumped out of the left ventricle with each heartbeat. A normal ejection fraction is 55-70%, between 40-55% indicates impairment, and <40% may be evidence of heart failure.

8 Tang et al, N Engl J Med 2010;363:2385-95.

CHF are 6.5 million and 600 thousand, respectively, which implies an addressable population of up to 2.3 million.[9] Underscoring the potential US market opportunity for Revascor, the AHA reports that CHF is responsible for c one million hospitalisations each year (AHA 2013), a figure unchanged from 2000 to 2010, and has total annual costs of c US$32bn (includes services, medications and lost productivity).[10]

Clinical – encouraging Phase II results in CHF

Initial findings from the US Phase II study in CHF were presented at the American Heart Association (AHA) meeting in late 2011, at which stage patients had completed mean follow-up of 18 months. Final results after 36 months of follow-up were announced in early 2013. The single-blinded, dose-escalation cohort trial evaluated the safety and efficacy of Revascor versus placebo in 60 patients with CHF of ischaemic (n=46) or non-ischaemic (n=14) origin. Enrolled patients were on maximal medical therapy (and possibly an ICD device), had mild-to-moderate symptoms (NYHA Class II-III) and impaired left ventricular ejection fraction (LVEF ≤40%).

The Revascor Phase II trial comprised three ascending dose cohorts (25m, 75m and 150m) with each group having 15 active patients and five controls. In each cohort subjects were randomised to receive either single intra-cardiac injection of Revascor, injected directly into left ventricular muscle (via transendocardial mapping and injection), or a mock mapping and injection procedure. While baseline patient characteristics were reasonably well balanced across the treatment groups, the control group included fewer ischaemic CHF patients (n=8) than the 25m (n=15), 75m (n=12) or 150m (n=11) cohorts. Control patients also had, on average, more severe CHF symptoms than the 150m group, but with broadly comparable LV impairment (Exhibit 5). Baseline imbalances are important to consider, in our view, given the small size of the individual treatment groups.

Exhibit 5: Baseline characteristics in Phase II CHF trial

	Control (n=15)	Revascor 150m (n=15)	P-value
Age (years)	62.7	62.7	
Ischaemic CHF	8 (53%)	11 (73%)	
NYHA class (mean)	2.6	2.2	0.03
MLHFQ (mean)	80.5	69.5	0.21
6MWT (mean)	319	361	0.33
LVEF – ECHO	34.6	34.3	0.92
LVEF – SPECT	36.5	36.3	0.96
LVEF – MUGA	31.6	28.4	0.23

Source: Edison Investment Research, Mesoblast. Note: MLHFQ = Minnesota Living with Heart Failure Questionnaire, BNP = Brain Natriuretic Peptide, 6MWT = 6 Minute Walk Test, ECHO = echocardiography, SPECT = Single Photon Emission Computed Tomography, MUGA = Multi Gated Acquisition Scan.

The Phase II trial met its primary endpoint for safety – Revascor was safe and well-tolerated across all doses, with no clinically relevant immune responses. Acknowledging the limitations of the trial design (single-blind, small size, baseline imbalances), preliminary efficacy data suggests that Revascor may improve clinical outcomes, as well as beneficially impacting heart function and functional exercise capacity. Results were most promising for the 150m dose:

- **Reduced cardiac deaths and heart failure hospitalisations** – at the interim (time-to-event) analysis, none of the 15 patients receiving 150m had experienced a heart failure-related major adverse cardiac event (HF-MACE; includes cardiac death, hospitalisation for decompensated heart failure, resuscitated cardiac death) after mean follow-up of 18 months, versus 27% (4/15) of controls and 27% (8/30) of the other dosage groups combined (Exhibit 6). There was no overlap of the 95% confidence intervals for time-to-first HF-MACE between Revascor 150m and other treatment groups, which points to this clinical benefit being significantly different. At the final analysis, no HF-MACE was seen in the 150m group after mean follow-up approaching 36 months, versus 33% (5/15) of controls.

9 Medicographia 2011;33:363-369.
10 Go et al, Circulation 2013;127:e6-245.

Exhibit 6: Phase II trial – time-to-first HF-MACE event

Endpoint	Revascor 150m	Revascor 75m	Revascor 25m	Control
Cardiac death, n	0	1	0	1
HF hospitalisation, n	0	4	2	3
Resuscitated VF, n	0	0	1	0
HF-MACE at 18 months, n (%)	0 (0%)	5 (33%)	3 (20%)	4 (27%)
HF-MACE at 36 months, n (%)	0 (%)	*5 (33%)	*3 (20%)	5 (33%)

Source: Perin & Borrow, Cell Therapy 2011; Mesoblast. Note: *Similar to 18-month results according to company.

- **Initial evidence of cardiac remodelling** – the Phase II trial included various measures of heart function – LVEF, LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV)[11] – at three, six and 12 months post treatment. At six months Revascor 150m showed reductions in LVESV (-27ml) and LVEDV (-30ml) vs control – these results hint at modest but beneficial effects on LV remodelling. However, LVEF was similar to control after six months (Exhibit 7).

Exhibit 7: Phase II trial – surrogate efficacy measures

	Revascor 150m	Revascor 75m	Revascor 25m	Control	Revascor 150m vs Control
LVEF (%) – 6 months	+0.9%	+0.5%	+3.7%	-1.2%	0.0
LVESV (ml) – 6 months	-7.3	+4.0	+19.9	+19.7	-27.0
LVEDV (ml) – 6 months	-9.7	+8.7	+34.5	+19.8	-29.5
6MWT (m) – 12 months	+50.8	+1.6	+19.4	-1.6	+52.4

Source: Perin & Borrow, Cell Therapy 2011

- **Trend to improved functional exercise capacity** – Patients receiving Revascor 150m showed a placebo-corrected 53m (p=0.06) increase in walking distance during the six-minute walk test (6MWT). Supporting this, recent results from the HF-ACTION study suggest that the 6MWT is prognostic for hospitalisation/mortality in NYHA class II and III systolic HF patients.[12]
- **Acceptable safety and tolerability** – Revascor was safe and well tolerated at all doses, with only one cardiac death after 22 months of follow-up. There were no clinically significant immune responses, with six (13%) of 45 Revascor patients developing transient (four, 9%) or persistent (two, 4%) anti-donor antibodies (against donor HLA class I). Persistent immune responses were only seen in 150m-treated patients, but were associated with no clinical signs or symptoms.

The Phase II data provide, in our view, preliminary evidence that Revascor 150m has concordant positive effects on clinical outcomes, cardiac remodelling and exercise capacity. We note, however, the lack of consistent dose-response (and statistical significance) across all endpoints, which could relate to the small patient groups and baseline patient imbalances. With the caveat that cross-trial comparisons are not scientifically valid, the efficacy of Revascor 150m – no cardiac deaths and c 30% difference in HF-MACE – compares favourably with incremental benefits offered by new CHF drugs or devices (CRT) (Exhibit 8).

The EMPHASIS-HF trial added eplerenone (Pfizer's Inspra) to standard medical therapy in NYHA class II patients: cardiac-related deaths were seen in 11% of eplerenone patients and 14% on placebo (relative risk-reduction of 24%) after median follow up of 21 months. The composite endpoint of cardiac death or HF hospitalisation (effectively HF-MACE) was seen in 18% and 26% patients, respectively (RR 37%). In the RAFT study, NYHA class II or III patients on optimal medical therapy were randomised to receive an ICD alone or ICD plus CRT. After average follow-up of 40 months, cardiac deaths were seen in 15% of ICD+CRT patients and 18% of ICD patients (RR

11 LVESV is the volume of blood in the left ventricle at the end of contraction (systole), as is used clinically as a measure of the adequacy of systolic function. LVEDV is the volume of blood in the left ventricle at end load (diastole). In systolic heart failure, the damaged left ventricle losses its ability to contract normally (reduced LVEF). Because the ventricle struggles to eject the blood contained within, the ventricular cavity size increases (adverse LV remodelling) with an increase in both end-diastolic and end-systolic volumes (ie increased LVEDV and LVESV).

12 Forman et al, J Am Coll Cardiol 2012 Dec 25; 60(25): 2653-61.

24%); on the composite endpoint of all deaths or HF hospitalisation, the figures were 33% and 40%, respectively (RR 25%).

Exhibit 8: Efficacy results in CHF trials

	Revascor 150m (Phase II)	CRT (RAFT)	Eplerenone 25mg (EMPHASIS-HF)
NYHA class (LVEF%)	II / III (<35%)	II / III (<30%)	II (<35%)
Mean follow-up (months)	36	40	22
Cardiac death			
Control-corrected difference (%)	7%	3%	3%
Relative risk reduction (%)	-	24%	24%
Heart failure hospitalisation			
Control-corrected difference (%)	20%	5%	6%
Relative risk reduction (%)	-	32%	42%
Death or hospitalisation			
Control-corrected difference (%)	33%	7%	8%
Relative risk reduction (%)	-	25%	37%

Source: Edison Investment Research, RAFT trial: Tang et al NEJM 2010;363, Emphasis trial: AHA presentation, 15 Nov 2010

Phase III trial – starting in Q413

The pivotal Phase III study is expected to start in Q413, following FDA clearance of the Investigational New Drug (IND), and 'first patient in' is expected by year-end 2013. Importantly, the trial protocol was designed after scientific input from both the FDA and EMA. Exhibit 9 outlines the Phase III trial design and endpoints. The trial is powered to detect a 25% relative reduction in the primary outcome (HF-MACE) – an assumed 20% event rate for controls and reduction to 15% for Revascor. These assumptions (control event rate, targeted relative reduction) mirror the results of recent CRT studies (ie RAFT) in similar patient populations (NYHA II/III, LVEF<35%).

Exhibit 9: Phase III trial design

	Details
Design	Multi-centre, randomised (1:1), double-blind, placebo-controlled trial to evaluate Revascor 150m in c 1,700 subjects with CHF. Primary endpoint is HF-MACE, with secondary efficacy measures of heart function and exercise capacity. Two interim efficacy and/or safety analyses: first analysis (not futility) after c 18 months will assess various efficacy and safety parameters to determine the risk/benefit ratio; second analysis (futility) on HF-MACE endpoint after c 30 months, at which time we expect majority (>60%) of patients to be recruited and c 40% of expected HF-MACE events.
Primary endpoint	Same as Phase II: time-to-event analysis of HF-MACE (includes cardiac death, resuscitated cardiac death, or non-fatal decompensated heart failure events). Study is powered to show a 25% relative reduction in primary endpoint (HF-MACE) for Revascor vs control – assumes c 20% event rate in controls and c 15% event rate on Revascor.
Patient population	Similar to Phase II study: NYHA class II and III systolic heart failure (LVEF≤40%) of ischaemic or non-ischaemic origin.
Territories	Initial recruitment in US, with European enrolment commencing in H214.

Source: Mesoblast, Edison Investment Research

Competing stem cell and gene therapies in late-stage trials

Exhibit 10 describes the competing stem cell and gene therapies in late-stage trials for CHF.

Exhibit 10: Selected stem cell and gene therapies in Phase II or III trials for CHF

Company	Product	Therapy class	Status	Target CHF patients	Notes
Mesoblast Teva	Revascor	Stem cell (allogeneic)	Phase III-ready	Ischaemic and non-ischaemic, NYHA II or III, LVEF<40	Allogeneic (bone marrow-derived) mesenchymal precursor cells (MPC). Phase III expected to start Q413.
Cardio3	C-Cure	Stem cell (autologous)	240-pt Phase III	Ischaemic, NYHA II to IV, LVEF<30%	Autologous (bone marrow-derived) cardiopoietic mesenchymal stem cells. Expected Phase III readout 2015.
Bioheart	MyoCell	Stem cell (autologous)	170-pt Phase II/III	Ischaemic (post AMI), NYHA II to IV, LVEF<35%	Autologous (skeletal muscle-derived) myoblasts. Expected Phase II/III readout Q114.
Celladon	Mydicar	Gene therapy	200-pt Phase IIb	Ischaemic or non-ischaemic, NHYA II to IV, LVEF<35%	Gene transfer using a viral vector (AAV1) to deliver the SERCA2a gene. Expected Phase IIb readout in Q116.
Aastrom	Ixmyelocel	Stem cell (autologous)	108-pt Phase II	Ischaemic, NYHA III or IV, LVEF<35%	Autologous (bone marrow-derived) CD90+ mesenchymal cells and CD14+ monocytes. Expected Phase II readout Q315.

Source: Edison Investment Research, Clinicaltrials.gov

Cardio3's C-Cure comprises autologous (patient bone marrow-derived) mesenchymal stem cells, which have been engineered to become new heart muscle cells; these 'cardiogenically oriented' stem cells are then delivered by endomyocardial injections to the left ventricle. The product was

advanced into the Phase III CHART-1 trial (start Q412; data Q414) based on results of the 45-patient Phase II C-Cure study, which added C-Cure to standard therapy in patients with ischaemic CHF (LVEF<40%, NYHA class II or III). Adjunctive C-Cure was shown to be safe as well as showing modest improvements in heart function (LVEF, LVESV, LVEDV), exercise capacity (6MWD) and composite clinical score (post-hoc analysis) at six months. The latter score included survival (marginally better for C-Cure) and hospitalisation (no difference vs control). The primary endpoint of CHART-1 is a hierarchical composite outcome at 39 weeks comprising – from most to least severe outcomes – time to death (all cause), HF events, quality of life (MLHFQ) and functional endpoints.

Forecasts – Revascor peak sales potential of US$4bn (A$4.4bn)

We assume US and EU approvals and launches in H119, based on Phase III trial duration of four years (start Q413; final data Q417). Our conservative 5% peak penetration (of addressable prevalence) assumes that Revascor is used as adjunct therapy in mild-to-moderate patients, with widespread adoption limited by price, cost of procedure and availability (tertiary referral hospitals). While final pricing/reimbursement will be determined by the strength of the Phase III data, our pricing of US$20,000 assumes Phase II findings are replicated by the pivotal trial. We believe this price is appropriate given the cost of HF hospitalisation, current pricing/reimbursement for ICD/CRT therapy, and estimated expenditure on combined CRT-ICD therapy (4-year average of $62,000).[13]

Exhibit 11: Revascor forecast assumptions in CHF

	US	Europe	Total	Notes
Addressable market – 2013 (m)	1.8	2.3	4.1	60% of CHF patients have systolic failure, of which 60% are NYHA class II or III.
Launch year (FY)	2019	2019		Assume Phase III start in H114, final data H117 (three-year trial duration), followed by US and EU approval and launch in H118.
Peak year (FY)	2024	2024		Peak sales at year six post launch.
Peak market share, n (%)	5%	5%		Conservative penetration assumption based on initial use as adjunct therapy, product price, procedure cost, and availability in specialist tertiary referral centres.
Pricing (US$)	20,000	15,000		Cost of HF hospitalisation in US is US$17-25k (source: CDC); US price of ICD c US$18k (Medicare reimbursement c US$11-20k); HF annual cost in Sweden >€11,000
Peak in-market sales by Teva (US$m)	2,127	1,935	4,062	ICD/CRT-D sales in US in 2010 were US$4.5bn. CRT-D sales expected to grow to US$2.8bn by 2015.
Peak revenues to MSB (US$m)	851	774	1,625	Assumes transfer price equivalent to 40% of net sales price

Source: Edison Investment Research

MPCs for acute myocardial infarction

Exhibit 12: Summary – MPCs for AMI

Rationale	Coronary artery infusion of MPCs directly after an AMI will protect 'at-risk' heart muscle cells from dying, thus limiting infarct size, decline in cardiac function and heart failure.
Dose/administration	Intracoronary (IC) infusion of a single dose of MPCs (12.5m or 25m cells) immediately after angioplasty and stent procedure
Clinical data	IC infusion of MPCs in animal model of AMI was safe and effective: smaller infarct size, improved perfusion, limited adverse remodelling, improved cardiac function.
Next news	Update on progress of 225-patient Phase II trial (2014).
Forecasts	Approval and launch in FY19; peak in-market sales of US$1.0bn (A$1.2bn).

Source: Edison Investment Research

Disease overview – risk of heart failure in AMI survivors

Acute myocardial infarction (AMI), or heart attack, occurs when the blood supply to the heart muscle is severely reduced or blocked. Prolonged interruption of blood flow (ischaemia) causes irreversible damage or death of heart muscle. AMIs are most commonly caused by the rupture of an atherosclerotic plaque within a coronary artery, which results in thrombosis (blood clot formation) that blocks the blood flow. AMI remains a leading cause of morbidity and mortality globally – it is associated with a c 25% mortality rate, with 15% of deaths occurring prior to hospitalisation and

13 Noyes et al, J Cardiovasc Electrophysiol 2013;24(1):66-74.

another 5-10% within a year (source: Medscape). The current standard care for AMI is percutaneous coronary intervention (stent) to open the artery and restore blood flow, alongside medical therapy to prevent further blood clots (antithrombotics), improve cardiac function (ACE inhibitors) and reduce risk factors (ie anti-hypertensives). Advances in interventional and medical therapy have reduced mortality rates for US hospitalised patients from c 15% in the 1980s to <5% currently. However, AMI survival often results in significant loss of cardiac function that may lead to CHF. This is due to post AMI changes in the size, shape and function of the left ventricle (LV), collectively termed adverse LV remodelling.

Market opportunity – 300k contestable patients in US

Mesoblast's Phase II trial is recruiting patients with *de novo* anterior AMI due to blockage of the left anterior descending (LAD) coronary artery. According to AHA, the annual incidence of AMI is 715k (607k new, 107k recurrent), with around 15% (c 107k) resulting in sudden death. Thus, there are c 600k 'surviving' AMI patients, of which we estimate c 50%[14] (300k) are primarily affected by LAD disease and potential candidates for MPC therapy. In Europe, we estimate the incidence of AMI at c 1m, resulting in a target population of 425k; as a cross reference, the British Heart Foundation (BHF) estimates that there are c 100k heart attacks in the UK every year.

Preclinical – positive data in multiple AMI models

Mesoblast's MPCs have shown preclinical efficacy in multiple animal models (sheep, pig and rat) of AMI. Most relevantly, intracoronary (IC) infusion of MPC in a large animal model of anterior AMI was shown to be safe, feasible and effective.[15] In this randomised study of 68 sheep, a single IC infusion of MPC significantly reduced infarct size (by 40%), abrograted adverse LV remodelling (lowere LV volumes), improved perfusion (>50% increase in blood vessel density) and improved cardiac function (12% increase in LVEF) versus control.

Clinical – update on Phase II study in 2014

An update on the ongoing Phase II safety study in AMI (AMICI) is expected in 2014. The multicentre (Australasian, European) randomised, placebo-controlled trial will enrol 225 subjects undergoing a stent procedure (to LAD) two to 12 hours after onset of symptoms. A single dose of MPCs (12.5m or 25m) or placebo is infused into the stented culprit artery. The primary endpoint is the frequency of MACCE events (includes cardiac death, AMI, target vessel revascularisation, stroke, new/worsening CHF following procedure, CHF hospitalisations) at 24 months. Other endpoints include infarct size and cardiac remodelling, which are evaluated at six and 12 months.

Forecasts – AMI peak sales potential of US$1.0bn (A$1.2bn)

Exhibit 13 outlines our forecast assumptions for MPCs in anterior AMI.

Exhibit 13: MPC forecast assumptions in AMI

	US	Europe	Total	Notes
Addressable market – 2013	300k	425k	725k	AHA statistics, BHF, NICE, European Society of Cardiology
Launch year (FY)	2019	2019		Positive Phase II data in 2015 could trigger Phase III development thereafter
Peak year (FY)	2024	2024		Peak sales at year six post launch.
Peak market share, n (%)	20%	20%		Penetration into new and recurrent anterior AMI population (LAD occlusion), with uptake driven by price, and availability in specialist tertiary referral centres.
Pricing (US$)	7,500	5,500		MPC dosing is 12.5m or 25m. Medicare reimbursement for PCI with coronary stent ranges from US$10,500 to US$18,500 (source: Abbott Vascular).
Peak in-market sales by Teva (US$m)	573	500	1,073	Global drug-eluting stent sales were c US$4.4bn in 2011 (Abbott's Xience US$1.5bn).
Peak revenues to MSB (US$m)	229	200	429	Assumes transfer price equivalent to 40% of net sales price.

Source: Edison Investment research

14 NYSHD (August 2012) www.health.ny.gov/statistics/diseases/cardiovascular/docs/pci_2008-2010.pdf.
15 Houtgraaf et al, Circulation Research, May 2013.

Spine: NeoFuse for lumbar spinal fusion

Exhibit 14: Summary – MPCs for lumbar spinal fusion	
Rationale	MPCs have osteogenic (bone-forming) potential and could provide an effective and safe alternative to existing spinal fusion products.
Dose/administration	A single dose of MPCs (25m or 75m cells) combined with a carrier material (MasterGraft Matrix) and placed in disc space between lumbar vertebrae.
Clinical data	Phase II data suggest comparable efficacy and safety to bone autograft, but avoids need for bone-harvesting procedure from patient's own hip.
Next news	Potential initiation of Phase III trial (2014).
Forecasts	Approval and launch in FY19; peak in-market sales of US$883m (A$962m).

Source: Edison Investment Research

Disease overview – surgery for severe lower back pain

Lumbar spinal fusion surgery is undertaken in patients who have severe lower back and/or neurological deficits that have not responded to conservative treatment. It is considered in conditions such as severe degenerative disc disease, spinal disc herniation and spondylolisthesis (slipped disc). Lumbar fusion fuses two of more lumbar vertebrae, eliminating motion between them and decreasing pain from the joint. Surgical approaches include posterior (PLIF, TLIF), lateral (LLIF) and anterior (ALIF). The surgeon places bone – autograft (from patient's hip) or allograft (donor bone or demineralised bone matrix [DBM]) – or a bone-replacement (bone morphogenic protein [BMP]) between the vertebrae. This stimulates the body's natural bone growth processes.

The standard against which all bone grafts (including Mesoblast's NeoFuse) are measured is autograft. However, because a second incision is required to harvest bone (from the hip), potential drawbacks include: poor candidate for harvesting (inadequate bone quality or quantity) longer surgical procedure, harvest-site infection, increased recovery time and long-term pain. Allograft bone carries the risk of infection or disease and the quality of the bone cannot be controlled.

Responding to these concerns, several companies (Medtronic, Stryker) developed synthetic versions of BMP, a naturally occurring protein that induces formation of new bone. Medtronic's InFuse (recombinant BMP-2) was FDA approved in 2002 for lumbar fusion (ALIF approach) and reached peak sales of c US$900m in 2011. However, InFuse sales have subsequently declined (c US$530m in 2012) due to increasing uncertainty about its benefit (over traditional bone autograft) and its safety. The emerging safety concerns relate to off-label use (life-threatening airway obstruction from cervical fusion) and increased cancer risk. A recent Yale review found that InFuse offered similar success to bone graft for lumbar fusion but had potential safety risks.[16]

Another alternative to traditional bone grafting is NuVasive's Osteocel Plus, an allograft "cellular matrix" that contains living bone cells (mesenchymal stem cells, osteoprogenitor cells) and a DBM scaffold. However, Osteocel is not FDA regulated (it came to market via the Human Cellular and Tissue Product [HCT/P] pathway) and, thus, did not undergo extensive clinical trials. In our view, the lack of FDA approval and supporting clinical data explains the product's modest sales since launch. In contrast, Mesoblast is undertaking a formal clinical trial programme (under an Investigational New Drug [IND] filing) to generative substantive data to support FDA premarket approval. This could, in our view, provide a major commercial advantage for NeoFuse if launched.

Market opportunity

An estimated 1.7m spinal fusion procedures were performed globally in 2011, of which 1m (c 60%) were lumbar fusions. The US represents the largest market with c 380k lumbar fusions undertaken in 2012.[17] We estimate that posterior approaches account for c 60% (228k) of procedures. In Europe, we estimate that c 350k lumbar fusions are undertaken annually, resulting in c 175k posterior approaches. As a cross reference for Europe, recent UK data (2010/11) indicates that

16 Fu et al, Annals of Internal Medicine 2013;158(12):890-902.
17 Millenium Research Group.

c 35k surgical procedures are undertaken annually in the NHS for back pain or radicular pain, the majority of which are lumbar fusions/decompressions.

In terms of other reference points, the global market for bone substitutes was estimated at c US$1.6bn in 2012, with spinal fusion procedures accounting for the majority (c 70%) of revenues. In the US, the market for bone substitutes was estimated at US$1.7bn in 2010, divided between allograft/DBM (US$700m), BMP (US$700m) and other agents (US$300m).[18] Sales of BMP have declined in recent years, from their peak of c US$900m, due to safety issues with InFuse.

Clinical – positive Phase II FDA trial

Results of the Phase II FDA study of NeoFuse in lumbar fusion were presented at the North American Spine Society (NASS) 2013 meeting. The prospective, multicentre, open-label study recruited 24 patients undergoing 1 or 2-level (ie two or three vertebrae) lumbar interbody fusion via posterior procedures (TLIF, PLIF). Enrolled subjects had degenerative disc disease (DDD) in the lumbar spine, clinical symptoms of neurogenic pain, and failed six months of conservative therapy. Patients were randomised to receive NeoFuse 25m (n=8), NeoFuse 75m (n=8) or autograft (n=8), with the latter taken from the patients hip (iliac crest).

Baseline patient characteristics were well balanced. Results from 23 patients were available at 12 months. Exhibit 15 summarises the main results of the study.

Exhibit 15: Phase II results in lumbar spinal fusion

Spinal fusion success	Comparable rates of fusion for all three groups, although NeoFuse 25m (seven patients, 86%) was slightly better than autograft (six, 75%) and NeoFuse 75m (five, 63%).
Pain relief	NeoFuse (both doses) and autograft offered similar improvements in back pain relief at 12 and 24 months.
Blood loss	Significantly lower (30-43%) reduction in blood loss versus autograft, although we view the absolute reduction (120-170ml) as unlikely to be clinically meaningful. The higher blood loss for autograft likely relates to the surgical harvesting of iliac crest bone.
Safety	No reoperations/revisions in any groups, similar AE rate across all groups, no treatment-related SAEs, no heterotopic (abnormal) bone formation, and no immune responses.

Source: Edison Investment Research

In summary, the data suggest that NeoFuse offers comparable efficacy and safety outcomes to autograft, but without requiring a second bone-harvesting procedure (and its associated risks). Based on these results, Mesoblast plans to initiate a pivotal Phase III study in 2014.

Forecasts – peak sales potential of US$883m (A$962m)

Exhibit 16 outlines our key model assumptions for NeoFuse in lumbar fusion.

Exhibit 16: NeoFuse forecast assumptions in lumbar spinal fusion

	US	Europe	Total	Notes
Addressable market – 2013	230k	170k	400k	US: Estimated 380k lumbar spinal fusions, of which 60% (230k) posterior approaches. EU: estimate 350k lumbar fusions, with 60% (175k) posterior.
Launch year (FY)	2019	2019		Assumes Phase III start in 2014, data 2017, submission 2018, approval/launch H119.
Peak year (FY)	2024	2024		Peak sales at year six post launch.
Peak market share, n (%)	40%	40%		Unmet need for alternative spinal fusion products that are safer (than Medtronic's InFuse), more convenient (than autografts) and better regulated (than Osteocel).
Pricing (US$)	5,000	3,750		MPC dose is 25m or 75m on carrier graft. Medtronic's InFuse (BMP-2) typically costs c US$5,000 in the US.
Peak in-market sales by partner (US$m)	590	293	883	Peak sales of InFuse were c US$900m. Global market for bone graft substitutes US$1.6bn in 2012 (70% from spinal fusions)
Peak revenues to MSB (US$m)	177	88	265	Assumes NeoFuse is partnered before/during Phase III trial. Forecast transfer price equivalent to 30% of net sales price.

Source: Edison Investment Research

18 IN VIVO November 2011;29(10).

Spine: MPCs for intervertebral disc repair

Exhibit 17: Summary – MPCs for intervertebral disc repair	
Rationale	Injecting MPCs into degenerated lumbar disc might stimulate regrowth of disc cartilage and restore normal disc function, thereby improving back pain/function and eliminating need for surgery.
Dose/Administration	A single intra-disc injection of MPCs (6m or 18m cells) in hyaluronic acid carrier.
Clinical Data	Interim Phase II results (50 patients at six months) suggest low-dose MPCs (6m) are safe and significantly improve back pain and function versus control injections.
Next news	Final Phase II results (all 100 patients at 12 months) in Q413.
Forecasts	Approval and launch in FY18; peak in-market sales of US$1.8bn (A$2.0bn).

Source: Edison Investment Research

Disease overview and market opportunity

Lower back pain affects up to 80% of people at some point during their lives. In the US, c 25% of adults experience an acute episode of back pain within a three-month period. Chronic lower back pain (over three months) can result from a wide variety of conditions including lumbar degenerative disc disease (DDD). Major risk factors for DDD are increasing age, genetics and mechanical injury/stresses to the disc. This leads to structural disruption and cell-mediated changes in disc composition. A degenerative lumbar disc can cause back discomfort, or more worryingly, press on the spinal nerves and cause pain, numbness, tingling or weakness in the leg(s). While the majority of patients are treated non-surgically (physiotherapy, analgesics, pain injections), more severe cases may require surgery (ie lumbar fusion). However, non-surgical treatments for DDD are only moderately successful – intra-disc injections of steroids provide only short-term relief.[19]

An estimated 30 million people in the US suffer from lower back pain, of which c 15% (c 4.5 million) fail to respond to conservative therapy (Frost & Sullivan, 2008). A proportion (c 500 thousand) has severe DDD that warrants surgery, which leaves c four million with limited options. We conservatively estimate that 25% (c one million) have moderate DDD that could be targeted with MPC injections.

Clinical data: Positive interim Phase II results; final data by end-2013

Mesoblast's preclinical work has shown that that intra-disc injections of MPCs can restore the extracellular matrix of degenerate discs. Based on these findings, Mesoblast is conducting a multicentre (US, Australian), randomised, double-blind, placebo-controlled Phase II trial in 100 patients with DDD. Enrolled subjects had chronic low back pain (>six months) due moderate DDD in the lumbar spine (from L1 to S1), which is unresponsive to three months of conservative therapy (including physiotherapy). Patients were divided into four groups to receive low-dose MPCs (6m, n=30), high-dose MPCs (18m, n=30), hyaluronic acid alone (n=20) or saline (n=20). The primary endpoint is safety with secondary efficacy endpoints including disc anatomy (MRI scan) and pain scores (visual analogue scale, VAS). Positive interim Phase II data were announced in April 2013. Results of this pre-specified analysis, which included 50 patients at the six-month timepoint, suggest low-dose MPCs could be effective.

Exhibit 18: Interim Phase II results in intervertebral disc repair	
Efficacy (pain, function)	Patients receiving low-dose (6m) MPCs showed significantly greater mean reduction in back pain vs hyaluronic acid alone (69% vs 38%, p=0.013), as well as significant functional improvement (51% vs 19%, p=0.013). Similar but non-significant trends were seen for 6m vs saline. In addition, the low-dose group showed significantly greater treatment success rates (71%) than high-dose (undisclosed), hyaluronic acid (20%) and saline (30%).[20]
Disc structure	No changes on MRI – disc morphology remained unchanged at six months relative to baseline in all four groups.
Safety	Good safety – no MPC-related SAEs. Low-dose MPCs showed lower rate of AEs than high-dose group (data not disclosed).

Source: Edison Investment Research

19 Muzin et al, Curr Rev Musculoskelet Med 2008; 1: 103-107.

20 Treatment success required patient to meet all the following criteria: clinically significant levels of improvement in back pain and function at six months vs baseline, maintenance or improvement in neurological status from baseline, maintenance of disc morphology compared to baseline as evaluated by MRI, and no serious adverse event or secondary intervention.

Final Phase II results (all 100 patients completing 12 months of follow-up) are expected by end-2013. Positive results could trigger the initiation of Phase III development in 2014.

Forecasts: Peak sales potential of US$1.8bn (A$1.9bn)

Exhibit 19 outlines our key model assumptions for MPCs in DDD.

Exhibit 19: MPC forecast assumptions in intervertebral disc repair

	US	Europe	Total	Notes
Addressable market – 2013	1m	1.5m	2.5m	
Launch year (FY)	2018	2018		
Peak year (FY)	2023	2023		Peak sales at year six post launch.
Peak market share, n (%)	20%	20%		Limited non-surgical treatment options for moderate lumbar DDD.
Pricing (US$)	5,000	3,750		MPC dose is 6m or 18m. Medtronic's InFuse (BMP-2) typically costs c US$5,000 in the US.
Peak in-market sales by Teva (US$m)	1,210	621	1,831	
Peak revenues to MSB (US$m)	363	186	549	Assumes product is partnered before/during Phase III development. Forecast transfer price equivalent to 30% of net sales price.

Source: Edison Investment Research

Immune: Prochymal for Crohn's disease

Exhibit 20: Summary – Prochymal for refractory moderate-to-severe CD

Rationale	MSCs have immunosuppressive capability without evidence of immunosuppressive toxicity, which could have utility in CD where there is uncontrolled immune system activation.
Dose/Administration	Multiple intravenous infusions (four times over two weeks) of MSCs (600m or 1,200m cells).
Clinical Data	Positive pilot Phase II data; positive interim analysis on Phase III trial.
Next news	Complete recruitment into Phase III study (2014).
Forecasts	Approval and launch in FY16; peak in-market sales of US$439m (A$478m).

Source: Edison Investment Research

Disease overview – treatment resistance a major issue

Crohn's disease (CD) is a form of inflammatory bowel disease (IBD), classified as an autoimmune disease, characterised by T-cell activation leading to tissue injury. It can affect any part of the gastrointestinal tract from the mouth to anus, with individuals experiencing periods of symptomatic relapse and remission. The cause is unknown and there is no cure. Tumour necrosis factor (TNF), a key inflammatory cytokine, is expressed prominently in IBD. As such, the development of biologic (anti-TNF) agents (ie AbbVies's Humira) has improved the induction and maintenance of remission in moderate-to-severe CD (CDAI[21] score 200-450). However, a significant proportion of patients fail to respond to anti-TNFs – clinical remission rates in the pivotal Humira studies were only 21-36%, with a similar proportion (36%) remaining in clinical remission after one year.

Market opportunity – 60k contestable patients in US

Based on US census data, an estimated 1.17m Americans have IBD including 565k with CD.[22] Furthermore, the prevalence of CD is gradually increasing, as expected for a condition without cure and low mortality. In terms of the addressable US market for Prochymal, we conservatively estimate that c 57k patients have moderate-to-severe CD that fails to respond to steroids and anti-TNFs.

Clinical – pilot Phase II data in treatment-resistant CD

Positive results a pilot Phase II study of Prochymal in CD were reported in 2006. The multi-centre (US), randomised, open-label trial recruited 10 patients with moderate-to-severe CD (average CDAI 340) who had failed prior steroids and anti-TNF therapy. Patients were divided into two groups to

21 Crohn's Disease Activity Index (CDAI) ranges between 0 – 600. Used to categorise severe disease (>450), moderate (200-450) and remission (<150). A 70-100 point change is clinically meaningful.
22 Kappelman et al, Dig Dis Sci 2013;58:519-525.

receive two infusions of low-dose (2m cells/kg) or high-dose (8m cells/kg) Prochymal and followed for 28 days. All patients showed a reduction in disease severity: average CDAI reduction of 62 points by day seven and a clinically meaningful reduction of 105 points by day 28. Patients receiving the higher dose showed a greater CDAI reduction (mean 137) than low dose (mean 65). Prochymal was also well tolerated and there were no SAEs.

Clinical – Ongoing US Phase III trial

An ongoing Phase III study is evaluating Prochymal in moderate-to-severe refractory CD. The multicentre (US), placebo-controlled, double-blind trial is evaluating Prochymal (either 600m or 1,200m cells) in 330 patients failing steroids and one anti-TNF. The primary endpoint is disease remission (CDAI score ≤150) at 28 days, with secondary measures including disease improvement (CDAI reduction >100 points).

We note that the Phase III programme has followed a complicated course – protracted (initiated 2007), interrupted (halted 2009, restarted 2010) and modified (one of two doses dropped, second maintenance trial stopped). Osiris halted enrolment in 2009 due to concerns that flaws in the trial design had spurred an unexpectedly high placebo response. However, an interim analysis of existing data suggested that Prochymal approached statistical significance on the primary endpoint (disease remission) in the ITT population. Following discussions with the FDA, patient enrolment was restarted at the best-performing (but undisclosed) dose arm and placebo. We expect the Phase III trial to complete enrolment in 2014 and deliver headline data in 2015. If results are positive, it remains unclear whether FDA will require a confirmatory trial.

Forecasts: Peak sales potential of US$439m (A$478m)

Exhibit 21 highlights our key model assumptions for Prochymal in CD (US market only).

Exhibit 21: Prochymal forecast assumptions in CD

	US	Europe	Total	Notes
Addressable market – 2013	56k	-	56k	US: prevalence of 565k, of which 10% (56k) have moderate-to-severe disease.
Launch year (FY)	2016	-		Assumes positive results from ongoing Phase III will garner FDA approval. Requirement for second confirmatory trial could push launch timelines back several years.
Peak year (FY)	2021	-		Peak sales at year six post launch.
Peak market share, n (%)	30%	-		High unmet need for treatments for refractory CD.
Pricing (US$)	20,000	-		Annual cost of anti-TNFs US$10-20k
Peak in-market sales by partner (US$m)	439	-	439	
Peak revenues to MSB (US$m)	132	-	132	Assumes product is partnered before/during Phase III development. Forecast transfer price equivalent to 30% of net sales price.

Source: Edison Investment Research

Immune: MPCs for rheumatoid arthritis

Rheumatoid arthritis (RA) is a progressive autoimmune disease characterised by cartilage and bone destruction associated with local production of multiple inflammatory cytokines, such as TNF-alpha and IL-17. The progression of RA is thought to involve multiple cells, including T cells and fibroblast-like synoviocytes in the synovium in inflammation and tissue damage. The worldwide prevalence of RA is c 1.5% of the adult population. However, the incidence remains relatively low with around 1.5 men and 3.6 women developing the condition per 10,000 per year.

Conventional treatment of RA relies on the use of corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) progressing to non-biologic disease modifying anti-rheumatic (DMARDSs) and biologic DMARDs for more difficult to manage cases. The potential therapeutic application of MPCs in RA is supported by evidence of a concomitant immune-modulatory effect on inflammation and autoimmunity through the inhibition of effector T cells.

Preclinical: Positive findings in large animal model

Preclinical results from a randomised, placebo-controlled study of 30 sheep with collagen-induced arthritis, an animal model that mimics joint damage characteristic of human RA, showed a reduction in TNF-alpha, IL-6 and IL-17 in the diseased joint when compared with saline-treated controls. Dosing in the study consisted of a single intravenous injection of 2m MPCs/kg and resulted in an 88% reduction in IL-6 levels (p=0.029), an 83% reduction in TNF-alpha levels (p=0.049), a 53% reduction in IL-17 levels (p=0.005), and a 43% reduction in infiltrating monocytes/macrophages (p=0.018). MPC-treated animals showed a 31% reduction in histopathology severity scores compared with controls (p<0.025). Positive preclinical data in sheep were incorporated in the IND application for the current Phase II trial.

Clinical: Ongoing Phase II trial in treatment-refractory RA

The ongoing US, randomised, 48-patient Phase II study is evaluating safety and efficacy of a single IV infusion of allogenic MPCs compared to placebo at 12 weeks post-infusion in patients with active rheumatoid arthritis. Patients in the study have received methotrexate ± other DMARDs for at least six months prior to screening and have had an incomplete response to at least one TNF-alpha inhibitor. The primary endpoint of safety will be based on the overall assessment of AE/SAEs, vital signs, physical examination, clinical laboratory tests, ECGs, pulmonary function rests and chest X-ray. Secondary endpoints demonstrating efficacy will be assessed using ACR 20/50/70, DAS28, ACR core response criteria. The final study readout is expected in H115.

Immune: MPCs for Type 2 diabetes & complications

Diabetic nephropathy (DN) is a complication of diabetes mellitus and a leading cause of chronic kidney disease (CKD). DN is typically characterised by angiopathy of the capillaries supplying the kidney glomeruli, which leads to declining filtering efficiency in the kidney and progressive loss in renal function. Type 2 diabetes accounts for 90% of the diabetic population worldwide. Approximately 20-30% of patients with diabetes (type 1 and type 2) develop evidence of nephropathy. The peak incidence of DN is approximately 3% of the diabetic population and typically presents 10-20 years after initial diagnosis of the condition. Incidence of CKD in the US, due to diabetes, is approximately 125,000.

Therapeutic interventions in diabetic nephropathy primarily seek to suppress inflammation and oxidative stress in order to reduce the decline in glomerular filtration rate (GFR) and stabilise kidney function. Current treatment focuses on underlying contributing factors such as hypertension using both angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).

Preclinical – positive data in multiple animal models

Preclinical studies in both diabetic and non-diabetic animal models of CKD suggest that intravenous administration of MPCs can modify both the inflammatory process and vascular endothelial dysfunction via the secretion of factors that enhance regeneration and repair of kidney tissue.[23]

Clinical – ongoing Phase II trials in type 2 diabetes and diabetic nephropathy

An ongoing, US, randomised, single-blind, 60-patient Phase I/II study assessing safety and tolerability of a single intravenous infusion of three doses of MPCs versus placebo in subjects with Type 2 diabetes patients with elevated blood glucose levels inadequately controlled on metformin.

[23] Lee RH, Seo MJ, Reger RL, et al. Multipotent stromal cells from human marrow home to and promote repair of pancreatic islets and renal glomeruli in diabetic NOD/scid mice; Ezquer F, Ezquer M, Simon V, et al. Endovenous administration of bone-marrow-derived multipotent mesenchymal stromal cells prevents renal failure in diabetic mice. Biol Blood Marrow Transplant 2009; 15(11): 1354-1365; Choi S, Park M, Kim J, Hwang S, Park S, Lee Y. The role of MSCs in the functional improvement of chronic renalfailure. Stem Cells Dev 2009.18 (3): 521-529.

The primary endpoint of safety of all three doses was made over three months of follow-up. Secondary endpoints of the study include assessment of glycaemic control (fasting blood glucose, HbA1c, fasting insulin, C-peptide), assessment of CRP and other inflammatory markers, and effects on end-organ function such as kidneys and heart. A review of the safety data from this trial supported an additional study of MPCs, using two selected doses, in diabetic nephropathy. A final readout in type 2 diabetes is expected in Q413.

An multicentre (Australian), randomised, double-blind, 30-patient Phase II study is evaluating the safety, tolerability and efficacy of a single intravenous infusion of two doses (150m and 300m) of MPCs versus placebo in subjects with diabetic nephropathy (stage 3b or 4). The primary endpoint of safety will be based on the overall assessment of AE/SAEs, vital signs, physical examination and clinical laboratory tests. Secondary endpoints include changes from baseline at 12 weeks of renal function (GFR, renal blood flow), serum creatinine, urinary albumin and protein excretion, glycemic-control and biomarkers. The study is expected to readout in September 2014.

Oncology: Prochymal for acute graft vs host disease

Exhibit 22: Summary – Prochymal for aGvHD

Rationale	Prochymal is intended to modulate adverse immune and inflammatory responses, repair damaged or diseased tissues and regenerate healthy tissue. Prochymal's activity against aGvHD, a T-cell mediated disease, is due to the immunomodulatory properties of MSCs.
Dose/administration	Paediatric aGvHD: multiple intravenous infusions (twice weekly for four weeks) of MSCs (2 x 10 MSC/kg)
Regulatory status	Conditional approval (Canada, New Zealand) for paediatric patients with steroid-refractory GvHD; available in US under Expanded Access Program for paediatric and adult patients with steroid-refractory GvHD.
Clinical data	Two Phase III trials missed their primary endpoints, but showed promising efficacy in patient subgroup with steroid-refractory gut and liver aGvHD. Positive results from 75-patient trial in paediatric severe aGvHD.
Next news	Outcome of regulatory discussions with FDA and EMA (2014) regarding potential filings in US and EU
Forecasts	Approval and launch in FY17; peak in-market sales of US$317m (A$346m)

Source: Edison Investment Research

Disease overview

Acute graft versus host disease (aGvHD) is a potentially life-threatening complication resulting from allogeneic hematopoietic stem cell transplantation (HSCT), a procedure most often performed for cancer patients (particularly leukaemia or lymphoma) but also for certain types of anaemia and immunological disorders. aGvHD can result from the activation of mature donor T-cells, which are co-infused with the HSC transplant (the graft) and attack the patient's body cells (the host), resulting in cytolytic effects that target several organs including the skin, gut and liver. Immunosuppressive agents, particularly IV steroids, are administered with HSCT, but treatment can be suboptimal and may increase the risk of opportunistic infections and disease relapse.

aGvHD arises in c 50% of all patients who receive HSCTs, but only c 50% of these respond to front-line steroids.[24] In patients with severe visceral (gut, liver) complications, mortality is c 90%. According to CIBMTR, GvHD is responsible for nearly 20% of deaths following allogenic HSCT.

Market opportunity – over 6,000 contestable patients in the US and EU

Approximately 22,000 allogenic HSCTs were undertaken globally in 2006.[25] In the US, more recent figures suggest that c 9,000 transplants are undertaken annually,[26] along with c 14,000 in Europe.[27] We estimate that 25,000 transplants (10,000 US, 15,000 EU) will be undertaken in 2013, of which 50% (12,500) experience aGvHD and 50% (6,250) fail steroids and are potential candidates for Prochymal. We note that the annual rate of allogenic HSCTs is increasing rapidly (doubling in EU over 2001-2011), so we project a rise to c 15,000 steroid-refractory patients by 2025.

24 Westin et al, Advances in Hematology 20 September 2011.
25 Gratwohl et al, JAMA 2010;303(16):1617-1624.
26 CIBMTR – Current uses and outcomes of HSCT 2012 (summary slides).
27 Passweg et al, Bone marrow Transplantation 2013, 15 April.

Clinical – Phase IIIs miss primary endpoints, but positive effects in visceral GvHD

Headline results from two Phase III studies of Prochymal in GvHD were announced in 2009:

- Front-line aGvHD (combined with steroids) – in this 192-patient trial (mostly skin GvHD), Prochymal showed no significant difference vs placebo (45% vs 46%) in the proportion of patients that had a complete response, no second-line therapy, and survived at least 90 days.
- Second-line aGvHD – in this 260-patient study (61 liver GvHD, 71 gut GvHD) Prochymal was similar to placebo (35% vs 30%) on the primary endpoint of complete response lasting at least 28 days. However, Prochymal showed significantly better durable complete responses in the subgroups with liver (76% vs 47%, p=0.026) and gut (88% vs 64%, p=0.018) GvHD. Also, data from the paediatric subgroup (n=28) showed a trend to improved responses (86% vs 57%).

Based on these results, Prochymal received conditional approval (Canada, New Zealand) for paediatric steroid-refractory aGvHD in 2012 but has not been launched in either territory. It is also available in the US under the FDA's Expanded Access Program (EAP) for the treatment of steroid-refractory GvHD in adults and children (used in c 60% of paediatric patients).

Recently published data suggest that Prochymal can significantly improve response rates and survival in children with severe, steroid-refractory aGvHD. The open-label study included 75 children with life-threatening aGvHD, who had received Prochymal under the EAP. This was a challenging population – 88% aggressive Grade C/D disease, failed three prior immunosuppressive agents, 91% major organ involvement (87% gut) – with poor survival prospects (c 5% at day 100). Results showed an overall response rate (complete + partial) of 61% at day 28, with responses seen across all disease grades and involved organs. Moreover, response to Prochymal at day 28 was a significant predictor of improved survival at day 100 (76% for responders vs 28% for non-responders, p<0.001). Prochymal was also safe and well-tolerated in this paediatric population.

Forecasts: Peak sales potential of US$317m (A$346m)

Backed by a growing body of supportive clinical data, Mesoblast will meet with the FDA and EMA in 2014 to discuss the potential development and regulatory requirements for Prochymal in aGvHD. The product has FDA designations as both an Orphan drug and fast track product. Pending updates, we assume FDA will request a further Phase III trial in subjects (adult and/or paediatric) with steroid-refractory visceral aGvHD. In terms of potential pricing, we note that Osiris indicated c US$200k in Canada; however, this was a small market opportunity (c 50 cases annually) and the product has not been launched. We model US$100k in the US and c US$75k in Europe.

Exhibit 23: Prochymal forecast assumptions in acute GvHD

	US	Europe	Total	Notes
Addressable market – 2013	10,000	15,000	25,000	Estimated 25,000 allogenic HSCTs (10k US, 15k EU) in 2013, of which 50% (12,500) develop GvHD and 50% (6250) fail first-line steroids.
Launch year (FY)	2017	2017		
Peak year (FY)	2022	2022		Peak sales at year six post launch.
Peak market share, n (%)	30%	30%		
Pricing (US$)	100,000	75,000		Reimbursed Canadian price potentially C$200,000 in paediatric setting. Assume lower price in model for US and EU.
Peak in-market sales by partner (US$m)	157	160	317	
Peak revenues to MSB (US$m)	47	48	95	Assumes product is partnered before/during Phase III development. Forecast transfer price equivalent to 30% of net sales price.

Source: Edison Investment Research

Oncology: MPCs for bone marrow transplantation

Mesoblast's ongoing Phase III study is using MPCs to expand umbilical cord-blood cells for transplantation in patients whose bone marrow has been destroyed by high-dose chemotherapy. The trial is being conducted together with Teva, which has global rights and financial obligations,

and (according to clinicaltrials.gov) is expected to render headline data in H118. However, we see potential for patient recruitment and the primary endpoint to be completed earlier than this timeframe. Poor engraftment due to low cell doses restricts the effectiveness of umbilical-cord-blood-transplantation. If the trial is successful, it could increase the number of unrelated transplants (by up to fourfold) by providing a treatment options for patients who cannot find a donor. We model an H119 approval and launch by partner Teva and peak in-market sales of US$250m (A$263m) with peak revenues to Mesoblast of US$100m (A$105m).

Initiated in July 2011, the multicentre, open-label study is randomising 240 patients to receive either MPC-expanded cord blood units (active arm) or unexpanded cord blood (control arm). The primary endpoint is the time to neutrophil and platelet recovery. Progression into Phase III was based on positive results of a 31-patient Phase I/II trial, which suggested that transplantation of MPC-expanded cord-blood cells was safe and effective in adults with haematologic cancers.[28] Expanded cord blood significantly improved engraftment: median time to neutrophil engraftment 15 vs 24 days with unexpanded cord blood; median time to platelet engraftment of 42 vs 49 days in control.

Financials

Mesoblast is a development stage biotech company and, on our forecasts, will generate its first meaningful product revenues from FY16. It is well capitalised (cash of A$315m at end-FY13) following a A$170m equity raise and has three (out of nine) ongoing Phase II/III programmes funded by partner Teva. Operating cash outflow (excluding interest income and tax) was c A$70m in FY13. Over the next two to three years, we expect the cash burn rate to increase (A$80-85m) as Mesoblast invests in clinical studies (potentially five Phase III trials starting or ongoing by end-FY14) and in commercial scale manufacturing processes for MPC and MSC production. In the absence of additional financing and/or partnerships, we estimate that Mesoblast's cash runway extends into late FY17. The key components of our P&L forecasts for FY14 and FY15 are as follows:

- **Revenues** – amortisation of the US$130m upfront payment from Cephalon results in FY14 and FY15 revenue estimates of A$16.2m. While Mesoblast reports interest payments on cash as revenue (as per Australian reporting standards), we include interest in the financing (net interest) line. We currently include no partnering revenue for the spinal indications, but assume that potential partners would fund all or part of Phase III trials and pay Mesoblast a transfer price equivalent to 30% of net in-market sales.
- **R&D tax credits** – Mesoblast's 'other income' line included R&D tax credits of A$5.9m in FY13. We currently exclude potential R&D tax credits in FY14 and FY15, pending company guidance.
- **COGS** – we do not expect Mesoblast to recognise any COGS until FY16 at the earliest. Mesoblast's COGS, which are paid to Lonza, increases as the size of the MPC dose increases. We reflect this in our model by linking COGS to net product revenue: our model calls for the company to record COGS of 10-15% on net sales by partner Teva (equivalent to 25-38% of transfer payment revenue recognised by Mesoblast).
- **Operating expenditure** – R&D: we forecast R&D spend of A$47.4m in FY14, rising to A$47.9m in FY15; G&A: we model annual G&A expenditure of A$32-33m in FY14 and FY15; Manufacturing & commercialisation – projected spend of c A$23m in both years.
- **Tax** – we do not expect Mesoblast to pay tax until FY16 at the earliest. All revenue will be recognised in the jurisdiction of the manufacturing facility (primarily Singapore) at a preferential tax rate (our working assumption is a low, long-term tax rate of 10%).
- **Shares** – Mesoblast had 317.4m shares in issue at end-FY13. The Osiris deal includes US$15m (A$15.6m) in stock payable upon transfer of assigned assets. We assume that 2.4m

28 De Lima et al, NEJM 2012;367:2305-2315.

shares (at A$6.50 each) will be issued by year-end 2013, resulting in weighted average shares for FY14 of 318.1m.

- **Share-based payments** – there were 10.8m share options outstanding on 30 June 2013 and we assume a similar number in FY14. This forms the basis our fully diluted share number of 330.5m at end-FY14.

Valuation

We value Mesoblast at A$2.6bn, or A$8.07 per share, based on a risk-adjusted net present value (rNPV) analysis. The breakdown of our rNPV model, which employs Edison's standard 12.5% discount rate, is shown in Exhibit 24. This also includes projected end-FY14 cash of A$211m. Edison's per share value is based on projected basic shares outstanding of 319.8m at end-FY14, which includes 2.4m shares issued as part of the Osiris deal. Our detailed forecast assumptions for key indications – CHF, AMI, intervertebral disc repair and lumbar fusion – have been outlined earlier in the note. We model cash flows for each product/indication from market launch through to loss of market exclusivity, which is broadly 12 years in the US and 10 in Europe. We currently model sales in US and EU markets only, so launches in additional territories (ie Japan) would offer pure upside.

We note that Edison's base-case rNPV, which represents c 30% upside to Mesoblast's current market capitalisation of A$2.0bn (A$6.30/share) is not a price target, but the fair value at which we believe the stock should be trading ahead of upcoming catalysts, including initiation of the Revascor Phase III trial by Teva (Q413), final Phase II results in intervertebral disc repair (Q413) and the potential start of Phase III development in disc repair or spinal fusion (H114). Initiation of recruitment into the Revascor Phase III trial (probability of success rises to 50%), which could assuage concerns about Teva's commitment, would see our rNPV rise to A$2.9bn (A$9.19/share). Positive disc repair data triggering Phase III start (probability of success rises to 50%) and spinal fusion Phase III initiation would increase our rNPV further to A$3.2bn or A$10.00/share.

Exhibit 24: Mesoblast valuation model

Product	Therapeutic area	Indication	rNPV (A$m)	rNPV/share (A$)	Prob. of success (%)	Launch (FY)	Peak sales (US$m)
MPC (Revascor)	Cardiovascular	Congestive heart failure (CHF)	1,434.3	4.49	40%	2019	4,062
MPC (Revascor)	Cardiovascular	Acute myocardial infarction (AMI)	231.5	0.72	25%	2019	1,073
MPC	Spine disease	Intervertebral disc repair	219.8	0.69	25%	2018	1,831
MPC (NeoFuse)	Spine disease	Posterior lumbar fusion	187.6	0.59	40%	2019	883
MPC	Immune	Diabetic nephropathy	121.4	0.38	20%	2020	1,815
MPC	Immune	Rheumatoid arthritis (RA)	86.1	0.27	20%	2020	1,350
MSC (Prochymal)	Immune	Crohn's disease (CD), US only	115.9	0.36	50%	2016	439
MPC	Oncology	Bone marrow transplantation	89.6	0.28	50%	2019	263
MSC (Prochymal)	Oncology	Acute graft versus host disease (GvHD)	88.3	0.28	50%	2017	317
R&D expenses			(92.1)	(0.29)			
Manufacturing expenses			(44.7)	(0.14)			
G&A expenses			(62.7)	(0.20)			
Net cash			210.7	0.66			
Total			**2,586**	**8.07**	**Basic**		
				7.82	**Diluted**		

Source: Edison Investment Research

CVS franchise – primary component of valuation

The cardiovascular indications for MPCs (CHF, AMI), which are covered by the Teva alliance, make up the majority of our rNPV. For Revascor in CHF, we apply a 40% probability of success pending the start of the Phase III trial (rises to 50% following announcement of 'first patient in'). For the remaining CVS indication, AMI, we assume a 25% probability of success given the stage (Phase II) and existing (preclinical) findings. Given that Revascor represents the largest component of our

valuation, we have conducted a scenario analysis to assess the impact of different price, market share, and risk adjustments on our rNPV (Exhibits 25 and 26).

Exhibit 25: rNPV (A$/share) with different Revascor price and penetration assumptions

		Price (US$)		
		15,000	20,000	25,000
Market penetration	2.5%	5.4	5.9	6.4
	5.0%	7.0	**8.1**	9.1
	7.5%	8.6	10.2	11.8

Source: Edison Investment Research

Exhibit 26: rNPV (A$/share) with different Revascor risk-adjustment and penetrations

		Probability of success (%)		
		30%	40%	50%
Market penetration	2%	5.0	5.5	6.0
	5%	6.9	**8.1**	9.2
	10%	10.2	12.4	14.6

Source: Edison Investment Research

Spinal programmes – upcoming value inflection points

We currently apply a 40% probability of success to MPCs in spinal fusion, given the efficacy and safety findings in the completed Phase II trial. We would expect to apply a 50% probability of success on commencement of Phase III in 2014. For intervertebral disc repair, we assume a 25% risk adjustment pending final data from the Phase II trial; positive data could also trigger initiation of pivotal development in 2014, unwinding our risk adjustment to 50%. As noted, we assume that both spinal indications are out-licensed during (or following completion of) Phase III development.

Immune indications – more speculative, but significant upside potential

We apply a Phase III (50%) probability of success to Prochymal in CD, although it remains unclear whether positive data from a single pivotal study will be sufficient to garner FDA approval. This risk is, in our view, reflected to some extent by limiting our valuation to the US market. We assign a lower (20%) probability of success to MPCs in RA and nephropathy, given the lack of existing clinical data in either indication.

Oncology products – niche indications, but meaningful rNPV contribution

Both BMT (MPCs) and acute GvHD (Prochymal) are orphan indications that could, if successful, provide meaningful upside to our valuation. We assume a 50% probability of success for both indications and peak sales ranging from US$263m (BMT) to US$317m (GvHD). We do not currently include Japanese Prochymal sales by JCR Pharma, so this could offer additional upside.

Sensitivities

Mesoblast is subject to the risks typically associated with biotech company drug development, including the possibility of unfavourable outcomes in clinical trials and regulatory reviews, success of competitors, and commercial decisions by partners or potential partners. The key stock specific sensitivities include:

- Teva alliance – this partnership underwrites the development and development of three major clinical programmes (CHF, AMI, BMT). While Teva has publically committed to funding the Revascor Phase III trial, and gained FDA approval to commence, we have limited insight into Teva's future strategic priorities (both R&D and commercial). However, we see little logic in Teva returning rights (given their significant equity stake), but see a possibility that it could monetise commercial rights should interim and/or final Phase III data be positive.
- Final Phase II results in intervertebral disc repair – while positive interim results may be indicative, they are not conclusive of the final trial results (which may be negative).
- Headline Phase II trial in AMI – initiation of this trial was not directly supported by prior clinical data, which adds an element of risk.
- Initial Phase II results in diabetes – while this is primarily a safety trial, lack of efficacy signals could be perceived as having negative read across to other IV indications (nepropathy, RA).

Exhibit 27: Financial summary

A$'000s	2011	2012	2013	2014e	2015e
Year end 31 December	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	116,221	27,808	24,185	16,176	16,176
Cost of Sales	0	0	0	0	0
Gross Profit	116,221	27,808	24,185	16,176	16,176
R&D Expenses	(11,948)	(36,937)	(43,108)	(47,419)	(47,893)
SG&A Expenses	(11,792)	(28,051)	(30,734)	(32,271)	(32,593)
EBITDA	90,238	(48,764)	(58,668)	(74,581)	(75,567)
Operating Profit (before amort and except)	90,103	(49,078)	(59,338)	(75,284)	(76,306)
Intangible Amortisation	(44)	(65)	(102)	(107)	(112)
Exceptionals	0	0	0	0	0
Share-based payments	(2,465)	(10,052)	(11,163)	(11,163)	(11,163)
Operating Profit	87,595	(59,195)	(70,603)	(86,554)	(87,581)
Net Interest	4,648	10,472	10,526	10,521	6,911
Profit Before Tax (norm)	94,751	(38,606)	(48,812)	(64,763)	(69,395)
Profit Before Tax (FRS 3)	92,243	(48,723)	(60,077)	(76,033)	(80,670)
Tax	(1,634)	(22,422)	(1,585)	0	0
Profit After Tax (norm)	93,117	(61,028)	(50,397)	(64,763)	(69,395)
Profit After Tax (FRS 3)	90,609	(71,145)	(61,662)	(76,033)	(80,670)
Average Number of Shares Outstanding (m)	216.8	282.9	292.8	318.1	319.8
EPS - normalised (c)	42.95	(21.58)	(17.21)	(20.36)	(21.70)
EPS - normalised and fully diluted (c)	40.88	(20.78)	(16.60)	(19.69)	(20.99)
EPS - (IFRS) (c)	41.79	(25.15)	(21.06)	(23.90)	(25.23)
Dividend per share (c)	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	100.0	100.0	100.0	100.0
EBITDA Margin (%)	N/A	N/A	N/A	N/A	N/A
Operating Margin (before GW and except) (%)	N/A	N/A	N/A	N/A	N/A
BALANCE SHEET					
Fixed Assets	497,755	503,877	551,868	552,389	552,874
Intangible Assets	475,326	497,219	547,834	547,834	547,834
Tangible Assets	609	1,998	2,757	3,278	3,763
Investments	21,820	4,660	1,277	1,277	1,277
Current Assets	265,495	216,579	331,844	227,260	151,380
Stocks	0	0	0	0	0
Debtors	2,101	10,669	12,063	12,063	12,063
Cash	263,228	205,591	315,309	210,725	134,845
Other	166	319	4,472	4,472	4,472
Current Liabilities	(30,794)	(44,495)	(50,588)	(37,484)	(37,484)
Creditors	(30,794)	(40,179)	(37,484)	(37,484)	(37,484)
Deferred revenue	0	(4,316)	(13,104)	0	0
Short term borrowings	0	0	0	0	0
Long Term Liabilities	(216,610)	(197,113)	(202,858)	(186,479)	(170,303)
Long term borrowings	(81,334)	(56,361)	(56,617)	(40,441)	(24,265)
Other long term liabilities	(135,276)	(140,752)	(146,241)	(146,038)	(146,038)
Net Assets	515,846	478,848	630,266	555,686	496,467
CASH FLOW					
Operating Cash Flow	108,229	(65,204)	(67,716)	(81,581)	(81,567)
Net Interest	2,790	9,308	10,338	10,521	6,911
Tax	0	(7,038)	3,297	3,000	0
Capex	(462)	(1,983)	(1,224)	(1,224)	(1,224)
Acquisitions/disposals	0	0	0	(35,300)	0
Financing	126,093	4,883	169,349	0	0
Dividends	0	0	0	0	0
Other	2,386	(3,015)	(3,818)	0	0
Net Cash Flow	239,036	(63,049)	110,226	(104,584)	(75,880)
Opening net debt/(cash)	(32,049)	(263,228)	(205,591)	(315,309)	(210,725)
HP finance leases initiated	0	0	0	0	0
Other	(7,858)	5,413	(508)	0	0
Closing net debt/(cash)	(263,227)	(205,592)	(315,309)	(210,725)	(134,845)

Source: Mesoblast accounts, Edison Investment Research

Contact details		Revenue by geography
Level 39, 55 Collins Street Melbourne 3000 Australia +61 3 9639 6036 www.mesoblast.com	Level 3, 505 Fifth Avenue New York, NY 10017 US + 212 880 2060	N/A

CAGR metrics		Profitability metrics		Balance sheet metrics		Sensitivities evaluation	
EPS 10-14e	N/A	ROCE 13	N/A	Gearing YY	N/A	Litigation/regulatory	◖
EPS 10-14e	N/A	Avg ROCE 09-14e	N/A	Interest cover YY	N/A	Pensions	○
EBITDA 10-14e	N/A	ROE 13	N/A	CA/CL YY	N/A	Currency	◖
EBITDA 10-14e	N/A	Gross margin 13	100%	Stock days YY	N/A	Stock overhang	○
Sales 10-14e	N/A	Operating margin 13	NA	Debtor days YY	N/A	Interest rates	○
Sales 10-14e	N/A	Gr mgn / Op mgn 13	NA	Creditor days YY	N/A	Oil/commodity prices	○

Management team

CEO and Managing Director: Professor Silviu Itescu

Prior to founding Mesoblast in 2004, Professor Silviu Itescu worked as a physician scientist in the fields of stem cell biology, autoimmune diseases, organ transplantation, and heart failure. He is an active faculty member of Melbourne and Monash universities in Australia and was previously a faculty member of Columbia University in New York. Professor Itescu has consulted for various international pharmaceutical companies, has been an adviser to biotechnology and health care investor groups, and has served on the board of directors of a number of publicly listed life sciences companies.

EVP, Global Therapeutic Products : Michael Schuster

Michael Schuster was a founding executive at Mesoblast prior to its public listing in 2004. He has led Mesoblast's product operational activities, and has been a member of the corporate executive leadership team developing the company's strategic, technical, and commercial plans. Mr Schuster also leads Mesoblast's investor relations outreach programme. He holds an undergraduate degree in science from Tufts University, a master's degree in immunology and microbiology from New York Medical College, and a master's of business administration from Fordham University in New York.

Chief Medical Officer : Dr Donna Skerrett

Dr Donna Skerrett, MD, has been involved in stem cell procurement, manipulation and transplantation for nearly 20 years. Her areas of expertise include conventional transfusion medicine, immunohematology, apheresis, histocompatibility testing, stem cell apheresis and processing, and novel regenerative medicine translational therapy. She is an advisor to the New York State Department of Health on the Progenitor Cell Committee and has been chair of the Governor's Council on Blood and Transfusion Services. Dr Skerrett joined Mesoblast in 2004.

Chief Financial Officer: Jenni Pilcher

Since qualifying as a chartered accountant with PricewaterhouseCoopers , Jenni Pilcher has worked in corporate and business financial roles for high-profile international companies in pharmaceuticals, fast moving consumer goods and services. Before joining Mesoblast in 2007, she spent six years with ASX 200 company Spotless Group, progressing through a variety of financial roles. Previously Mrs Pilcher worked in the finance teams at Cadbury Schweppes and international pharmaceutical group Medeva, both based in the UK. She was appointed CFO of Mesoblast in November 2007 and company secretary in January 2012.

Principal shareholders	(%)
Professor Silviu Itescu	21.5
Teva Pharmaceuticals	17.6
Prudential	10.1
Thorney Holdings	5.6
Capital	3.3
Blackrock	2.2

Companies named in this report

Teva Pharmaceutical Industries (NYSE:TEVA), JCR Pharmaceuticals (TYO:4552), Lonza Group (VTX:LONN), Aastron Biosciences (NASDAQ:ASTM).

Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
245 Park Avenue, 39th Floor
10167, New York
US

Sydney +61 (0)2 9258 1162
Level 33, Australia Square
264 George St, Sydney
NSW 2000, Australia

Wellington +64 (0)48 948 555
Level 15, 171 Featherston St
Wellington 6011
New Zealand