EDISON

International Stem Cell

Initiation of coverage

Seeking a better treatment for Parkinson's

Pharma & biotech

International Stem Cell (ISCO) is an early-stage cell therapy company currently in Phase I/IIa clinical trials to treat Parkinson's disease (PD). In addition, ISCO sells skincare and biomedical supplies to the market, generating $8m in sales and $1.7m in underlying operating profit in 2015. The commercial businesses provide a floor under ISCO's current valuation, creating an essentially free option on the PD candidate.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/14	7.0	(8.7)	(9.71)	0.0	N/A	N/A
12/15	7.6	(4.6)	(1.29)	0.0	N/A	N/A
12/16e	8.2	(5.5)	(1.96)	0.0	N/A	N/A
12/17e	9.0	(5.8)	(2.07)	0.0	N/A	N/A

Note: *PBT and EPS are normalized, excluding amortization of acquired intangibles, exceptional items and share-based payments.

Better stem cells = better therapeutic potential?

ISCO's technology platform is based on human parthenogenetic stem cells (hpSCs). Parthenogenetic stem cells are created from unfertilized human eggs (oocytes) chemically activated to make the cells pluripotent. As hpSCs express fewer parental histocompatibility antigens, they reduce the risk of immune rejection.

Parkinson's: A significant problem with no cure

As many as 2-3 million people suffer from PD in the US and EU, according to the Parkinson's Disease Foundation (PDF), and there are currently no approved treatments to slow or halt progression of the disease. If ISCO's treatment proves effective at slowing or halting disease progression, we forecast potential peak sales of $2.8bn based on 2% of existing and 5% of newly diagnosed patients in the US and 1-2% of patients in the EU and RoW receiving treatment.

Commercial business reduces risk

ISCO's commercial operations leverage its hpSC technology and generate revenues to partially offset R&D spending for therapeutic development. Lifeline Skin Care (LSC) develops and sells skincare products and Lifeline Cell Technology (LCT) produces human cell culture products for testing.

Valuation: $9.60 per basic share, but dilution a risk

Using a risk-adjusted NPV model, we value the company at $27m or $9.60 per basic share, using a 12.5% discount rate and a 7.5% probability of success for the PD candidate and a 10% discount rate and 90% probability for the skincare and biomedical businesses. Under the current capital structure, there are c 19m additional shares from convertible preferred stock, options and warrants on top of 2.8m current common shares, potentially leading to significant dilution for minority investors. In addition, the company's convertible preferred shares are subject to anti-dilution protection, creating further dilution potential, and we predict an additional $76m in future financing needs.

16 May 2016

Price	**US$2.51**
Market cap	**US$7m**

Net cash ($m) at 31 December 2015	0.5
Shares in issue	2.8m
Free float	60.1%
Code	ISCO
Primary exchange	OTC
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(37.4)	2.9	(69.1)
Rel (local)	(36.3)	(6.3)	(68.3)
52-week high/low	US$8.04		US$1.8

Business description

International Stem Cell is an early-stage biotechnology company developing therapeutic, biomedical and cosmeceutical applications for its proprietary stem form of pluripotent stem cells – human parthenogenetic stem cells (hpSCs). Its lead candidate is a cell therapy treatment for Parkinson's disease.

Next events

March quarter results	May 2016
Phase I preliminary data	Q416

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Edison profile page

Investment summary

Company description: A broad stem cell platform

International Stem Cell (ISCO) is an early-stage biotechnology company developing therapeutic, biomedical and cosmeceutical applications for its proprietary form of pluripotent stem cells – human parthenogenetic stem cells (hpSCs). ISC California (the predecessor to ISCO) was created in 2006 and went public in December 2006 through a reverse merger, changing its name to International Stem Cell in January 2007.

With its hpSC technology, ISCO has created 15 stem cell lines to develop different cell types: liver cells, neural cells and three-dimensional eye structures. The company's technology platform does not require the use of fertilized eggs, embryos or foetal tissue to create stem cells, improving product cost and consistency while reducing the controversy associated with other types of stem cells. Its lead candidate is a set of neural cells currently undergoing Phase I/IIa clinical testing for Parkinson's disease (PD). The company's portfolio includes preclinical candidates to address ischemic stroke and spinal cord injuries, metabolic liver disease, and retinal and corneal blindness.

ISCO's commercial operations leverage its hpSC technology and generate revenues to partially offset R&D spending for therapeutic development. LSC develops and sells skincare products and LCT produces human cell culture products for testing.

Valuation: $9.60/share

We value ISCO based on a risk-adjusted net present value (rNPV) methodology, using a 10% discount rate and 90% probability for the skincare/biomedical businesses and a 12.5% discount rate and 7.5% probability for the PD candidate, due to its early development stage. Our model does not ascribe any value to the rest of ISCO's therapeutic pipeline as the projects are largely dormant while the company focuses on its lead candidate. Our rNPV value is $27m, or $9.60 per share on an undiluted basis.

Financials: Dilution risk dominates

The company had $0.5m in cash on the balance sheet at 31 December 2015. This was supplemented with a March 2016 offering that provided $2.5m in cash and extinguished $3.8m in debt ($6.3m total proceeds). Its cash burn is just over $0.5m/month and likely to increase as clinical trials progress. Minority investors should note that under the current capital structure, there are c 19m potential common shares from convertible preferred stock, options and warrants that are outstanding, on top of the 2.8m common shares outstanding, which potentially creates sizeable dilution. In addition, the company's convertible preferred shares are subject to anti-dilution protection, creating further dilution under an array of circumstances. We project financing needs as illustrative long-term debt of $76m by 2023, with an estimated $13.5m required by 2017.

Sensitivities: Significant, but not insurmountable

As with any early-stage biotechnology company, ISCO faces numerous risks and uncertainties, especially preclinical risk. The investment case rests largely on the successful execution of the PD cell therapy clinical trials and the company's ability to attract a licensing/development partner to continue clinical development and, if approved, commercialization. The company's therapy for PD is in Phase I/IIa human trials and, due to its early-stage nature, has not been shown definitively to be efficacious. However, preclinical data showed improvements in both dopamine production and stable Parkinson's factor scores (ParkScore) in a primate study. Another risk stems from the capital structure, which, as mentioned, potentially creates sizeable dilution risk for minority investors.

Company description: A lasting treatment for PD?

International Stem Cell (ISCO) is an early-stage biotechnology company developing therapeutic, biomedical and skincare applications for its proprietary form of pluripotent stem cells – human parthenogenetic stem cells (hpSCs). With its hpSC technology (see below), ISCO has created 15 stem cell lines, each of which is a different HLA type. From this, it creates different cell types such as liver cells, neural cells and three-dimensional eye structures. Its lead candidate is a set of neural cells currently undergoing Phase I/IIa clinical testing for Parkinson's disease.

Stem cell basics and ISCO's proprietary hpSC technology

According to the Michael J. Fox Foundation, stem cell research has the potential to have a significant impact on the development of disease-modifying treatments for PD and considerable progress has been made in creating dopamine-producing cells from stem cells.

There are two naturally occurring types of stem cells, each with their own positives and negatives:

- **Embryonic stem cells** (ESCs) are controversial in many jurisdictions as they cannot be obtained without destroying a fertilized embryo. ESCs come from four- to five-day-old embryos created during in vitro fertilization procedures, but not implanted. These unused embryos or blastocysts can continue to be stored (at a cost to the patient) but are often donated for research or destroyed. ESCs require specific signals to differentiate into the desired cell type. If they are simply injected into a patient, they will differentiate into many different types of cells, possibly resulting in a tumour.
- **Adult stem cells** have been used for years in bone marrow therapy. Their use in research and therapy is not as controversial as the use of ESCs, because the production of adult stem cells does not require the destruction of an embryo.

Engineering stem cells

A key focus of stem cell research is the development of pluripotent stem cells – stem cells that can be coaxed to become virtually any type of cell in an organism. There are two key types of engineered pluripotent stem cells.

Induced pluripotent stem cells (iPSCs) are engineered from older, fully specialized cells such as skin cells. Scientists encourage these limited cells to act like embryonic stem cells again, with the ability to become any type of human cell. This is a complex technique that has only recently been developed and is the subject of much ongoing research.

Parthenogenetic stem cells are created from unfertilized human eggs (oocytes) activated by chemical or physical means (parthenogenesis) to make the cells pluripotent. Activation results in a parthenote from which pluripotent parthenogenetic stem cell lines can be derived and further differentiated into specific cell types.

ISCO's technology platform is based on hpSCs differentiated using chemical means. There are several techniques for turning an oocyte into a parthenote. One example uses a chemical catalyst such as $SrCl_2$, ethanol, Ca^{2+} ionophore, or ionomycin. This is followed by another chemical, for instance 6-DMAP (a broad protein synthesis inhibitor) or cytochalasin B or D (inhibitors of actin filaments polymerization), which blocks second polar body (PB2) extrusion. Thus, the resulting parthenote is a "pseudodiploid" heterozygous embryo containing the two sister chromatids of each maternal chromosome present in the MII oocyte.

Basic parthenogenetic cells are expanded, characterized and cryopreserved into a master cell bank under cGMP conditions. These cells are then chemically directed to differentiate into a pure population of neural stem cells (ISC-hpNSC) under feeder-free conditions. The differentiated cells

are then grown in an incubated environment, characterized for the presence of neural markers and the lack of pluripotent markers, and tested for microbial and viral contaminants before being used.

Currently ISCO owns the largest published collection of human parthenogenetic stem cell lines (hpSCs) with 15 lines total; each line can be differentiated into multiple cell types. According to the article Parthenogenesis and Human Assisted Reproduction (Bos-Mikich et al, Stem Cells International 2016): “the therapeutic use of pluripotent stem cells, such as human embryonic stem cells (hESCs) or phESCs, is still in its infancy. The wider application of hESCs is limited due to their genetic background, which will most likely be divergent from a potential patient. phESCs may overcome this limitation presented by hESCs in autologous histocompatible transplantations, as they should be isogenic with the gamete donor.”

Parkinson’s disease – manageable until it isn’t

Parkinson’s disease is a progressive, irreversible neurodegenerative disorder. It arises from a lack of dopamine in the brain, owing to the death/damage of dopamine-generating cells in the substantia nigra located deep in the mid-brain just above where the spinal cord connects to the brain. The cause of cell death is currently unknown.

According to the PDF, as many as 7-10 million people are affected by PD worldwide. The American Parkinson Disease Association estimates there are around 1.5 million Americans with PD; the PDF estimates there are nearly one million US patients, with 60,000 diagnosed a year. The European Parkinson’s Disease Association estimates there are around 1.2 million patients affected in Europe. Prevalence increases with age, with the typical age of onset more than 50 years old.

Treatments and their limitations

PD patients are evaluated using the Unified Parkinson Disease Rating Scale (UPDRS), which consists of three parts: mentation, behavior, mood; activities of daily living; and motor symptoms. Of a total possible score of 199 points (0 = no disability, 199 = worst/total disability), motor symptoms can account for just over half (108 points at worst) of the patient rating. When patients begin to take L-DOPA, motor improvements of 25% (off-patient baseline so -7 points on an initial baseline of 28) have been cited. However, long-term studies suggest that after four or five years patients see modest improvement (6 points on the UPDRS scale) on L-DOPA compared to baseline.

There are a number of different classes of therapeutic molecules available for PD; however, these therapies only address the symptoms and do not slow or halt progress of the disease. The main families of drugs useful for treating motor symptoms are levodopa, dopamine agonists and MAO-B inhibitors.

Levodopa is one of the most commonly used treatments for PD symptoms. However, after five to 10 years of treatment, between 50-70% of PD patients develop levodopa-induced dyskinesia (LID), which is characterized by involuntary random and jerky movements similar to those motor symptoms for which the levodopa was originally prescribed. Current management includes adjusting levodopa dosing and/or adding a dopamine receptor D2 agonist to the regimen to spare levodopa. Amantadine (Symmetrel by Endo Pharmaceuticals), an NMDA receptor antagonist, is the only orally active drug on the market that can be prescribed without special monitoring to improve PD-LID, although it can induce side effects including dizziness.

When medications are not enough to control symptoms, surgical techniques such as deep brain stimulation (DBS) can relieve the associated movement disorders; however, patients undergoing DBS frequently develop side effects such as short-term memory loss.

Exhibit 1: Select currently marketed drug therapies for Parkinson's disease

Company name (originator)	Product names	Description	Comments/regulatory designation
AbbVie Inc.	Duodopa, Duopa, levodopa/carbidopa	Levodopa-carbidopa intestinal gel	US – orphan drug (treat Parkinson's disease).
Boehringer Ingelheim GmbH	Mirapex, Mirapex ER, Mirapexin, Sifrol, pramipexole (pexola)	Dopamine agonist	In one of the two early PD studies (n=335) the mean improvement from baseline on the UPDRS Part III total score was 5.0 in the MIRAPEX arm vs -0.8.
Vernalis (Stada Arzneimittel AG in Japan)	Apokyn	Combines melevodopa, a methyl ester prodrug of levodopa, with carbidopa	Three blinded clinical studies (n=29, 17, 62) showed statistically significant benefit of Apokyn vs placebo on UPDRS motor scores (improvement of 20-24pt off baseline averaging 40).
GlaxoSmithKline	Adartel, Requip, ropinirole (Adartrel)	Dopamine D2 and dopamine D3 receptor agonist	Requip trial on early PD patients without L-DOPA (n=63) showed 30% improvement in UPDRS motor score on responders vs placebo. Similar results vs placebo from two other studies.
Impax Laboratories	Numient, Rytary, carbidopa/levodopa (IPX066, GSK587124, Patrome)	Extended-release capsule formulation of carbidopa, an inhibitor of aromatic amino acid decarboxylation, and levodopa, an aromatic amino acid	US – Special Protocol Assessment (treat PD) EU – Standard Review (treat idiopathic PD). Clinical study of advanced PD patients showed statistically significant reduction in "off" periods for motor symptoms, 6.1 hr vs 3.9 hr at baseline.
Biotie (to be acquired by Acorda Therapeutics)	Nouriast, istradefylline (KW-6002)	Adenosine A2A receptor (ADORA2A) antagonist	US – Special Protocol Assessment (treat idiopathic PD as adjunctive therapy to levodopa/carbidopa) The average daily "off" time for individuals receiving tozadenant at the 120mg dose decreased by 1.9 hours (5.9 hours per day at baseline to 4.0 hours at 12 weeks).
Newron Pharmaceuticals	Xadago, safinamide (PNU-151774E)	Alpha-aminoamide derivative that acts as a reversible monoamine oxidase B (MAO-B) and dopamine reuptake inhibitor while reducing glutamatergic activity	EU – Standard Review (treat PD); Complete response letter received FDA March 2016.
Novartis	Stalevo, Comtan, entacapone	Catechol-O-methyl-transferase (COMT) inhibitor that inhibits breakdown of levodopa	Study data show improvement in "on" time (no symptoms) vs placebo (p=0.001). Approximately 15% improvement in UPDRS motor score (p<0.05).
Orion Corp	Eldepryl, selegiline	Selective monoamine oxidase B (MAO-B) inhibitor	Patients treated had a 13% reduction from baseline in daily "off" time, compared with a 5% reduction for patients treated with placebo.
Roche	Tasmar (tolcapone)	Catechol-O-methyl-transferase (COMT) inhibitor that inhibits breakdown of levodopa	Adjuct therapy only.
Teva Pharmaceutical Industries	Agilect, Azilect, rasagiline (mesylate)	Irreversible selective inhibitor of monoamine oxidase B (MAO-B)	Study showed 15% improvement in UPDRS motor score at 1mg dosage as monotherapy.
Valeant Pharmaceuticals.	Zelapar, selegiline	Monoamine oxidase B (MAO-B) inhibitor	

Source: BioCentury, Edison Investment Research

Competitive pipeline for Parkinson's disease

Much of the advanced small molecule pipeline for PD focuses on enhancements to existing therapies such as ways to provide more consistent delivery of levodopa. However, the clinical challenge may be that the mechanisms of L-DOPA in the brain are more complicated than originally believed. For example, L-DOPA is released on an intermittent or as needed basis in the brain, not at a consistent level. In addition, the oral dosage of L-DOPA needed to achieve therapeutic benefits is considerably higher than would be needed under more direct delivery methods, which may contribute to long-term L-DOPA resistance. However, there are several drug candidates in the pipeline for L-DOPA-induced dyskinesia, which, if effective over the long term, may reduce or delay the need for more expensive and invasive therapies.

There are several cell therapy and gene therapy treatments looking to address the cause of Parkinson's. Cell therapies introduce new neural cells to supplement or replace cells damaged or destroyed by the disease. According to BioCentury, there are currently six cell therapy candidates for PD in the pipeline from discovery to Phase II, of which the most advanced is Living Cell Technologies' NeutrophinCell (NTCELL), an implantable choroid plexus cell product that contains specialized brain cells, which produce and secrete neurotrophins and cerebrospinal fluid (CSF). In a Phase IIa clinical study, NTCELL was injected in four patients under guidance by neuroimaging into the affected area of the brain. NTCELL decreased UPDRS by an average of 16 points after 58 weeks, representing a three- to four-year reversal of neurological deterioration.

Exhibit 2: Selected candidates for L-DOPA induced dyskinesia

Company name (originator)	Latest stage of development	Description	Therapeutic modality	Milestones/comments
Addex Therapeutics	Phase II	Immediate-release formulation of dipraglurant, a negative allosteric modulator of mGluR5	Small molecule	No results posted.
Laboratoires Pierre Fabre	Phase II	Serotonin (5-HT1A) receptor agonist	Small molecule	No results posted.
PsychoGenics	Phase II	Selective serotonin (5-HT1A) receptor and 5-HT1B receptor partial agonist	Small molecule	US – orphan drug (treat PD levodopa-induced dyskinesia [PD-LID]). Start Phase IIb (2016).
Adamas Pharmaceuticals	Phase III	Oral extended-release formulation of amantadine	Small molecule	US – orphan drug (treat levodopa-induced dyskinesia in patients with PD). Submit NDA 2016.
Osmotica Pharmaceutical	Phase III	Extended-release formulation of amantadine	Small molecule	US – orphan drug (treat levodopa-induced dyskinesia in patients with PD). Submit NDA 2016.

Source: BioCentury, Edison Investment Research

Gene therapy seeks to repair damaged neurons or coax the body into creating new neural cells, as opposed to adding new neural stem cells as in cell therapy. BioCentury lists seven gene therapy candidates in development for PD. Furthest along in gene therapy research is Voyager Therapeutics' VY-AADC01, for advanced PD with human POC expected in H216. VY-AADC01 is an AAV serotype 2 vector encoding dopa decarboxylase (DDC; AADC) that is delivered to the posterior putamen using image-guided, convection-enhanced delivery (CED) to treat PD. VY-AADC01 is in an actively recruiting, open-label Phase Ib trial.

Exhibit 3: Selected clinical-stage cell and gene therapy candidates in PD

Company (originator)	Stage of development	Description	Therapeutic modality	Milestones/comments
Living Cell Technologies	Phase IIa	Choroid plexus cell product that secretes neurotrophins and cerebrospinal fluid (CSF)	Cell therapy	Phase IIb start Q116; NTCELL decreased UPDRS by an average of 16 points after 58 weeks, representing a three- to four-year reversal of neurological deterioration.
International Stem Cell	Phase I	Neuronal cells derived from human parthenogenetic stem cells (hpSC)	Cell therapy: Stem cell	Phase I preliminary data (Q416).
uniQure NV	Phase I	Adeno-associated viral (AAV) vector carrying the glial cell-derived neurotrophic factor (GDNF) gene	Gene therapy: Viral vector: Adeno-associated virus (AAV)	The aim of this clinical trial is to introduce GDNF in a targeted way to the brain to enhance outcomes. NIH research at UCSF with option to license.
Voyager Therapeutics	Phase II	Adeno-associated virus (AAV) serotype 2 encoding the dopa decarboxylase (DDC; AADC) gene injected into the putamen	Gene therapy: Viral vector: Adeno-associated virus (AAV)	Phase Ib data (H216).
Oxford BioMedica	Phase I/II	LentiVector carrying 3 genes encoding enzymes for dopamine synthesis	Gene therapy: Viral vector: Lentivirus	Preclinical studies in the industry standard in vivo model of Parkinson's disease have shown that, following a single treatment, almost complete recovery of movement behavior was achieved after five to eight weeks. Therapeutic effect was statistically significant (p<.0.05) after two weeks and was maintained throughout the duration of the preclinical studies, with the latest time point being 44 months.

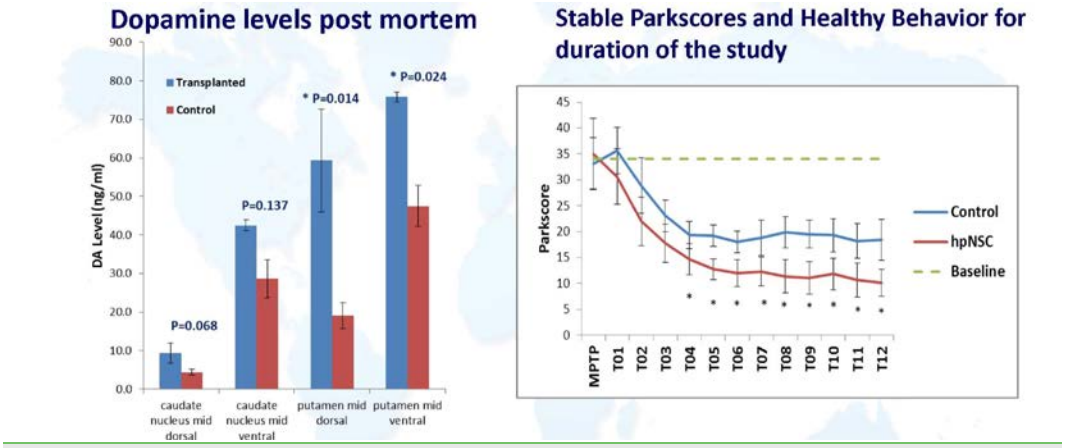
Source: BioCentury, Edison Investment Research

ISCO's clinical development program

ISCO presented results of its PD preclinical studies in October 2015 at Neuroscience 2015 in Chicago. The preclinical studies on 18 non-human primates showed that at 12 months, the transplanted cells had integrated into the dopamine fibres and dopamine levels post-mortem were significantly higher in the transplanted group versus the control group.

On 7 March, ISCO began enrolment in its Phase I clinical study for PD. The Phase I clinical study is a dose escalation safety and preliminary efficacy study of ISC-hpNSC, intracranially transplanted into patients. The procedure is invasive. Doctors create an opening in the skull and deliver the cells into the deep brain via an injection over a four- to five-hour period. As with other studies that involve cell transplantation into the brain, patients may suffer adverse effects such as wound infection and ischemia at the transplantation site among others.

Exhibit 4: ISCO preclinical data



Source: International Stem Cell presentation

The open-label, single-center, uncontrolled clinical trial will evaluate three different dose regimens of 30-70m neural cells. A total of 12 participants with moderate to severe Parkinson's disease will be treated. Patients must be between 30 and 70 years of age. Patients will be monitored to evaluate the safety and biologic activity of ISC-hpNSC for a year. A PET scan will be performed at baseline, as part of the screening assessment, and at six and 12 months after surgical intervention. Clinical responses compared to baseline will be evaluated using various neurological assessments such as UPDRS, Hoehn and Yahr and other rating scales. The study will be performed at Royal Melbourne Hospital in Australia. If the pilot proves successful, larger Phase II trials will start in 2017 or 2018 in Australia, Europe and the US. As ISCO operates a fully licensed tissue bank with GMP, it will not require additional certification to produce cells for these additional trials.

We do not anticipate sales from ISCO's PD therapy until 2024, with the company identifying a licensing partner sometime after Phase II trials. Our model includes a 50/50 share of R&D costs for the PD product between ISCO and its licensee, milestone payments of $10m in 2021, $15m in 2022 and $30m on US FDA approval (anticipated in 2024) and a 12% royalty on sales to ISCO. Our model calls for the licensee to assume or reimburse ISCO for PD production costs, which, according to ISCO's management, are currently in the range of $1,000-2,000 per treatment. We also anticipate that the licensee will assume all marketing and distribution costs.

We assume a treatment price of $20,000 (excluding surgical costs) in the US and $15,000 outside the US. We look for first year sales of $16.8m in 2024 based on 993 patients treated worldwide, at an average price of c $17,000, resulting in royalties of just over $2m to ISCO. We forecast peak sales in 2032 of $2.8bn, based on treatment of 176,927 patients (approximately 1.5% of the PD population) at an average price of c $16,000 resulting in royalties to ISCO of $334m. Our peak sales number for the US in 2032 equates to approximately nine surgeries pa for each of the c 4,900 neurosurgeons in the US. According to the World Health Organization (WHO), in 2004 there were 33,193 neurosurgeons in 103 countries surveyed. On our 2032 peak procedure number of 176,927, this equates to 5.3 procedures per surgeon pa. We note that ISCO's treatment is invasive, requiring surgeons to create an opening in the skull to administer the cell therapy directly into the brain. The invasiveness may limit market acceptance if there are less invasive options available.

Cosmeceutical and biomedical business lines

Lifeline Skin Care (LSC) develops, manufactures and markets a line of luxury skincare products sold in the US and internationally through a branded website, professional channels (including

dermatologists, plastic surgeons, medical, day and resort spas) and a network of distributors including Amazon and DermStore.

Exhibit 5: Lifeline Skin Care product line

Product	Description	Price	Benefit claims
Daily defense complex	Moisturizer/day cream	$160/1oz	■ Helps to diminish the appearance of fine lines and wrinkles. ■ Helps prevent dehydration and replenishes moisture.
Molecular renewal serum	Treatment cream	$210/0.5oz	■ Firms and tones skin for a smoother surface. ■ Upregulation of hyaluronic acid increases moisture channelling. ■ Micro-molecular delivery penetrates more easily.
Recovery night moisture serum	Treatment cream	$190/1oz	■ Reduces appearance of fine lines and wrinkles; slows the appearance of ageing. ■ Visibly lifts, firms and tones skin by replenishing and protecting the skin's moisture barrier. ■ Increases moisture levels to soften the skin and promote elasticity.
Eye firming complex	Eye cream	$97/0.5oz	■ Dramatic improvements in the visible signs of ageing above and below the eyes. ■ Immediate tightening benefits and reduces the appearance of puffiness.
Neck firming complex	Neck treatment cream	$180/1oz	■ Minimizes discoloration and redness of skin for a more even looking tone. ■ Boosts collagen production.
Brightening cleanser	Face wash	$37/1.7oz	■ Ultra-fine powders release salicylic acid and rice enzymes that micro-exfoliate dull, dry, dead skin cells, instantly leaving skin smoother and brighter. ■ Anti-oxidants help reveal brighter, more even skin tone. ■ Salicylic acid causes the uppermost layer of skin to soften and then peel, removing dead skin cells.
Refresh polishing gelee	Exfoliating face wash	$32/3.3oz	■ Gentle exfoliation of dead skin cells.
Dual action exfoliant	Glycolic exfoliator	$32/1.7oz	■ Glycolic acid and microcrystals safely remove dead skin cells revealing brighter, younger-looking skin. ■ Soothing ingredients leave skin with a smoother look and feel.

Source: Company website

Products sold include cleansers, exfoliators and a range of specialized moisturizers and serums. LSC is a very small player in the $111bn global skincare market (source: Euromonitor), but its focus on Asia-Pacific and premium-priced skincare products has enabled it to grow faster than the 3.3% CAGR for the overall market. The skincare division grew revenues at a CAGR of 17% in 2012-15, reporting revenues of $3.5m in 2015, flat vs 2014, and operating margins of 11.9%.

Exhibit 6: Commercial business segment reported financials

$000s	2013	2014	2015
Revenues			
Skin care	3,204	3,507	3,503
Biomedical	2,943	3,510	4,048
Total	6,147	7,017	7,551
Operating expenses			
Skin care	2,914	3,253	3,087
Biomedical	2,579	2,749	2,794
Total	5,493	6,002	5,881
Operating margins			
Skin care	9.1%	7.2%	11.9%
Biomedical	12.4%	21.7%	31.0%
Commercial business operating margin	10.6%	14.5%	22.1%

Source: International Stem Cell 10k

Lifeline Cell Technology (LCT) develops, manufactures and commercializes over 130 human cell culture products, including frozen human "primary" cells and the reagents (called media) needed to grow, maintain and differentiate the cells. Cell types include endothelial, epithelial, fibroblasts, melanocytes, stem and smooth muscle among others. Products are sold through the company's website. According to a 2015 survey by Lab Manager, sales of life sciences reagents/chemicals have been the fastest growing part of the laboratory products industry, growing an estimated 6.6% in 2014. Over 2012-15, revenue from ISCO's biomedical business grew at a CAGR of 19%, or nearly 3x the industry rate. ISCO's biomedical division had sales slightly above $4m in 2015, up 15% from 2014. Operating margins were just over 31% in this business in 2015, up from 21.7% in 2014 and 12.4% in 2013. We assume the margin expansion is due to efficiencies of scale.

Sensitivities

Development risk: the company's therapeutic products are still in Phase I and patient recruitment has just begun. In addition, the science behind stem cell therapies is in its infancy, with researchers studying not only how to produce cells reliably, but also how stem cells may work in various therapies.

Financing and partnership risk: ISCO will continue to need new capital to conduct operations and develop its therapeutic products for the foreseeable future. Its cash burn in 2015 was approximately $0.53m/month; however, the commercial operations offset the cash burn by approximately $0.13m/month. ISCO will seek to out-license its cell therapy treatment for PD following the completion of Phase I/IIa studies in the 2018 time frame, although we believe potential partners will seek additional confirmation before licensing the product. The timing of any partnership agreement, along with related milestones, will affect our valuation model.

Dilution risk: to date, ISCO has relied primarily on a combination of convertible preferred shares, warrants and options to fund its growth. While management has not converted or sold its sizeable holdings (and says that it does not intend to), investors need to consider the possibility of significant dilution risk at some point in the future. Currently, there are 19m potential common shares from convertible preferred stock, options and warrants that are outstanding, on top of the 2.8m common shares outstanding. Investors should note that the convertible preferred shares are subject to anti-dilution provisions under certain circumstances, creating further dilution potential.

Exhibit 7: Potential dilution

Derivative	Dilutive shares	Weighted average exercise price
Options	1,283,303	$19.66
Warrants	11,286,201	$2.57
Convertible Preferred Stock	6,798,592	$2.50
Stock incentive plans	12,679	N/A

Source: International Stem Cell. Note: Exercise prices accurate as of S-1 filed on 20 April 2016.

Management voting control: management controls approximately 70% of the total voting power of the company, which may deter some investors.

Stem cell regulatory risk: stem cell research is controversial and is currently subject to intense scrutiny. Any future legislation that is unfavorable to the development of hESC technology, hpSC technology, or nuclear transfer technology could adversely affect ISCO's operations.

Valuation

Our model calls for the skincare business to grow to sales of $4.8m by 2025, while the biomedical business grows to $10.5m over the same period. Sales in both businesses will be driven by overall growth in their respective industries (discussed in more detail in the Financials section), as well as modest market share gains in these multi-billion dollar global business segments. On a combined basis, before corporate G&A, we forecast a profit margin in the high teens to low 20s, peaking at 23% in 2025.

As the first human trials are still ongoing, we have narrowed our primary treatment population to those with newly diagnosed disease (5% by 2030 in the US and lesser amounts in the EU and RoW) and a smaller portion (1-2%) of patients with existing disease. We are forecasting peak sales of $2.8bn in 2032, resulting in peak royalty revenues to ISCO of $334m, in addition to $55m in milestone and upfront payments.

We value ISCO based on a risk-adjusted net present value (rNPV) methodology with a 10% discount rate and assign a 90% probability to the commercial (skincare and biomedical) businesses

and a 12.5% discount rate and 7.5% probability to the PD therapy given its early stage of development. Our model does not ascribe any value to the rest of ISCO's therapeutic pipeline, as the projects are largely dormant while the company focuses on its lead candidate. Our intrinsic value is $27m, or $9.60 per share. Our valuation reflects cash of $0.5m at 31 December.

Exhibit 8: rNPV valuation model

Product	Status	Launch	Peak sales ($m)	NPV ($m)	Probability	rNPV ($m)	NPV/share ($/share)
Cosmetic and biomedical business	Commercial	Current	22	29	90%	26	9.3
Parkinson's disease (royalties at 12% of sales)	Phase I/IIa	2024	2,800	408	7.5%	31	10.9
G&A expense – after tax					100%	(30)	(10.8)
Net cash				1	100%	1	0.2
Valuation				437		27	9.6

Source: Edison Investment Research estimates

We examined peer multiples for the skincare and biomedical businesses to estimate how those businesses might be valued on a standalone basis. P/Es on latest earnings for consumer products and cosmetics companies span a wide range from the high teens for Nu Skin Enterprises (18x) to the high 20s/low 30s for Estee Lauder (30x), Revlon (34x) and L'Oréal (26x). In the laboratory supply business, P/Es on latest earnings range from the low double digits for Enzo Biochemical (14x) to the high 20s/low 30s for Agilent Technologies (30x).

Financials

Our model calls for revenues in the cosmetic/skincare business to grow from $3.5m in 2015 to $4.8m by 2025, a CAGR of 3.2%, in line with the 3.3% CAGR estimate for the global skincare market from Euromonitor.

According to a 2015 survey by Lab Manager, sales of life sciences reagents/chemicals have been the fastest growing part of the laboratory products industry, growing an estimated 6.6% in 2014. In 2012-15, ISCO's biomedical business (which consists of cells and reagents/chemicals) grew at a CAGR of 19%, or nearly 3x the industry rate. We look for revenues in this business to grow at a CAGR of 10% through 2025. Operating margins were just over 23% in this business in 2015. On a blended basis, we forecast operating margins (excluding corporate G&A) for the combined skincare/biomedical supply business in the high teens to low 20s, peaking at 23% in 2025.

We expect the company to post a loss of $5.5m in 2016, growing to $15.0m in 2022 as it moves into costly Phase II/III trials. We expect the company to start generating profit from 2024. We project financing needs as long-term debt of $76m by 2023. These financing needs include our assumptions of a 50% R&D cost share with any potential licensing partner and milestones of $10m in 2021, $15m in 2022 and $30m on US FDA approval. However, we note that the company has so far used preferred equity to cover costs. On 20 April, ISCO filed an S-1 registering 8m of the underlying common shares from the March private placement. Under the current capital structure, there are c 19m potential common shares from convertible preferred stock, options and warrants that are outstanding, on top of the 2.8m common shares, creating sizeable dilution potential.

Exhibit 9: Private placement details

Issue	Description	Number issued	Issue price/share	Conversion price	Shares at conversion	Comment/expiration
Series I	Convertible preferred	6,310	$1,000	$1.75	3.5m	Subject to anti-dilution provisions
Series A	Common stock purchase warrants	N/A	N/A	$3.65	3.6m	Five years
Series B	Common stock purchase warrants	N/A	N/A	$1.75	3.6m	Six months
Series C	Common stock purchase warrants	N/A	N/A	$1.75	3.6m	Twelve months

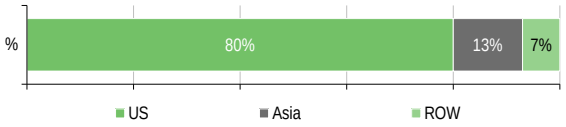
Source: International Stem Cell

Exhibit 10: Financial summary

US$000	2013	2014	2015	2016e	2017e	2018e
December	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP
PROFIT & LOSS						
Revenue	6,147	7,017	7,551	8,167	9,043	9,924
Cost of Sales	(1,643)	(1,921)	(2,056)	(2,205)	(2,442)	(2,580)
Gross Profit	4,504	5,096	5,495	5,962	6,601	7,344
Research and development	(3,560)	(5,386)	(2,707)	(4,000)	(4,000)	(6,000)
EBITDA	(8,010)	(9,138)	(5,036)	(5,524)	(5,218)	(6,811)
Operating Profit (before amort. and except.)	(7,546)	(8,680)	(4,564)	(5,052)	(4,746)	(6,339)
Intangible Amortization	0	0	0	0	0	0
Exceptionals	0	0	0	0	0	0
Other	(2,930)	(3,796)	1,929	0	0	0
Operating Profit	(10,476)	(12,476)	(2,635)	(5,052)	(4,746)	(6,339)
Net Interest	(3)	(2)	0	(480)	(1,080)	(1,680)
Profit Before Tax (norm)	(7,549)	(8,682)	(4,564)	(5,532)	(5,826)	(8,019)
Profit Before Tax (reported)	(10,479)	(12,478)	(2,635)	(5,532)	(5,826)	(8,019)
Tax	0	0	0	0	0	0
Profit After Tax (norm)	(10,479)	(12,478)	(2,635)	(5,532)	(5,826)	(8,019)
Profit After Tax (reported)	(10,479)	(12,478)	(2,635)	(5,532)	(5,826)	(8,019)
Average Number of Shares Outstanding (m)	0.8	1.3	2.0	2.8	2.8	2.8
EPS - normalized (US$)	(12.77)	(9.71)	(1.29)	(1.96)	(2.07)	(2.85)
EPS - normalized and fully diluted (US$)	(12.77)	(9.71)	(1.29)	(1.96)	(2.07)	(2.85)
EPS - (reported) (US$)	(12.77)	(9.71)	(1.29)	(1.96)	(2.07)	(2.85)
Dividend per share (US$)	0.0	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	73.3	72.6	72.8	73.0	73.0	74.0
EBITDA Margin (%)	N/A	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	N/A
BALANCE SHEET						
Fixed Assets	3,113	3,563	4,147	4,541	4,953	5,383
Intangible Assets	2,250	2,795	3,223	3,690	4,157	4,624
Tangible Assets	830	714	864	791	736	699
Investments	33	54	60	60	60	60
Current Assets	4,626	3,616	2,991	6,354	7,742	6,921
Stocks	1,369	1,517	1,348	1,458	1,614	1,772
Debtors	306	453	539	583	645	708
Cash	2,243	1,111	532	3,740	4,911	3,869
Other	708	535	572	572	572	572
Current Liabilities	(7,021)	(6,858)	(5,544)	(2,504)	(2,631)	(2,758)
Creditors	(7,021)	(6,858)	(5,544)	(2,504)	(2,631)	(2,758)
Short term borrowings	0	0	0	0	0	0
Long Term Liabilities	0	0	0	(6,000)	(13,500)	(21,000)
Long term borrowings	0	0	0	(6,000)	(13,500)	(21,000)
Other long term liabilities	0	0	0	0	0	0
Net Assets	718	321	1,594	2,391	(3,435)	(11,454)
CASH FLOW						
Operating Cash Flow	(5,638)	(6,413)	(4,120)	(4,645)	(4,366)	(5,960)
Net Interest	(3)	(2)	0	(480)	(1,080)	(1,680)
Tax	0	0	0	0	0	0
Capex	(896)	(988)	(738)	(866)	(884)	(901)
Acquisitions/disposals	0	0	0	0	0	0
Financing	8,123	6,270	1,169	2,500	0	0
Dividends	0	0	0	0	0	0
Net Cash Flow	1,586	(1,133)	(3,689)	(3,492)	(6,330)	(8,541)
Opening net debt/(cash)	(657)	(2,243)	(1,111)	(532)	2,260	8,589
HP finance leases initiated	0	0	0	0	0	0
Other	0	1	3,110	700	(0)	0
Closing net debt/(cash)	(2,243)	(1,111)	(532)	2,260	8,589	17,131

Source: International Stem Cell reports, Edison Investment Research estimates. Note: Estimates do not include conversion of convertible preferred stock.

EDISON

Contact details	Revenue by geography
5950 Priestly Drive, Carlsbad, CA 92008 US +1 760 940 6383 www.internationalstemcell.com	

Management team

Co-chairman and Chief Executive Officer: Andrey Semechkin, PhD

Dr Semechkin has over 20 years of experience creating and managing businesses ranging from startups to multi-billion dollar market cap companies, across different industries and scientific sectors. He is a specialist in system analysis, strategic planning and corporate management. Dr Semechkin is a member of the Russian Academy of Sciences.

Executive VP and Chief Scientific Officer: Russell Kern, PhD

Dr Kern was trained in medical genetics, embryology and stem cell biology. He was part of the team, along with scientists from the NYU Medical School, that elucidated the physiological changes that occur in the brains of Parkinson's disease patients. Dr Kern is a well-known speaker on stem cell biology, including the use of stem cells for neurology and skin regeneration. He has more than 40 publications in the field of Parkinson's disease and stem cell biology.

Chief Financial Officer: Mahnaz Ebrahimi, CPA

Ms Ebrahimi has more than 25 years of experience in financial management and accounting of growing research-driven companies in the life sciences, biotechnology, and pharmaceutical sectors. Most recently, she has been assisting several biotechnology and technology companies on accounting and SEC related matters in an expert consultancy capacity, including Flux Power Holdings, Polaris Pharmaceuticals and Ocera Therapeutics. Ms Ebrahimi served as director of finance and planning, as well as treasury, of eBioscience from 2010 until its acquisition by Affymetrix in June 2012.

VP Legal Affairs and Operations: Sophia Garnette, JD

Ms. Garnette received her JD from the University of Miami School of Law and has experience in various aspects of corporate and biotechnology law, regulatory affairs, project management, and business operations. After joining the company in March 2011, she has held a variety of business and legal roles, including in-house counsel, advisor to the CEO, and vice chairman of the board of directors for Lifeline Skin Care. Ms Garnette holds a bachelor's degree in economics from San Francisco State University and worked in the finance industry prior to beginning her legal career.

President of Lifeline Cell Technology, LLC: Francisco Bustamante

Mr Bustamante has over 18 years of experience in operations of biotechnology companies, including senior management positions in the areas of manufacturing, procurement, planning, warehousing, distribution and project management. He has an excellent understanding of the manufacture and logistics of cell culture products, biological instruments, molecular biology kits and diagnostics. He has led key projects in the areas of manufacturing resource planning (MRP) systems implementation, ISO compliance and product development. His industry experience includes Clonetics, BioWhittaker (Cambrex), Digene and Meso Scale Diagnostics. Mr Bustamante received his BS degree in biology from the University of San Diego and his MBA degree from Frostburg State University. He has been with Lifeline Cell Technology since 2007.

Director, CMC: Glenn Sherman, PhD

Dr Sherman has over 20 years of experience in regulatory affairs. He worked as a primary microbiology reviewer at the US FDA where he led pre-IND reviews in the Division of Antiviral Drug Products. After leaving the FDA, Dr Sherman held regulatory positions at Pfizer and Johnson & Johnson, where he was CMC regulatory lead for biologics products and successfully managed IND related activities for the biologics clinical, nonclinical and CMC teams. Dr Sherman holds a PhD in microbiology and immunology from the University of North Carolina, Chapel Hill, NC.

Principal shareholders (Common shares)	(%)
Andrey Semechkin	27
Russell Kern	5
Don Wright	0.4
Charles Casamento	0.4

Companies named in this report

Living Cell Technologies (LCT), Mesoblast (MSB), Voyager Therapeutics (VYGR), Endo Pharmaceuticals (ENDP), NuSkin Enterprise (NUS)s, Agilent Technologies (A), Estee Lauder (EL), Enzo Biochemical (ENZ), Revlon (REV), Elizabeth Arden (RDEN)

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