OvaScience

Initiation of coverage

Edison investment research

On fertile ground

Pharma & biotech

OvaScience is developing novel treatments for female infertility. The company's near-term investment case effectively rests on the successful development and commercialisation of its lead product, AUGMENT, to improve the success rate of *in vitro* fertilisation (IVF). If study results are positive and AUGMENT retains its lower-risk regulatory status, we project peak US sales of $160m/year. The technology underpinning AUGMENT and OvaTure (preclinical) is based on the landmark scientific discovery of egg-producing stem cells (egg precursor cells, EggPC) in human ovaries.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS (p)	P/E (x)	Yield (%)
12/11	0.0	(2.3)	(2.50)	0.0	N/A	N/A
12/12e	0.0	(12.8)	(1.62)	0.0	N/A	N/A
12/13e	0.0	(15.8)	(1.11)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding intangible amortisation and exceptional items.

Harnessing egg-producing stem cells

The US market for IVF is worth c $2.5bn and growing (4% CAGR 2005-10), despite its relatively low success rates, potential risks and high costs. OvaScience's lead product candidate, AUGMENT, is designed to improve the success rate of IVF, where procedure numbers are growing due to delayed childbearing and rising infertility awareness. Second candidate, OvaTure, holds potential to improve or replace IVF. Both programmes are based on the novel and patented EggPC technology platform.

AUGMENT targets growing unmet need

The AUGMENT procedure adds a woman's own EggPC mitochondria to her egg during IVF, which could improve egg quality and success rates. AUGMENT builds on earlier, supportive human studies of cytoplasmic/mitochondria transfer. Positive results from the AUGMENT study (results H214) could trigger a US commercial launch in H214. Provided the procedure is safe, shows clinically relevant efficacy and retains its lower-risk regulatory status, peak US sales could be >$160m/year in the initial indication (women requiring donor eggs or those aged >35 failing multiple IVF cycles).

OvaTure holds potential to transform IVF

OvaTure harnesses a woman's own EggPC to create mature eggs for use in IVF. This might restore fertility (i.e. post chemotherapy), extend the age limit for pregnancy, reduce the use of donor eggs and eliminate the need for hormonal hyperstimulation. Positive preclinical data (H114) could trigger the initiation of human trials in 2015.

Valuation: Risk-adjusted NPV of $146m

We value OvaScience at $146m, or $10.20 per share, based on a risk-adjusted NPV analysis. Our rNPV model, which includes AUGMENT plus net cash, represents upside to the current share price of $8.50. Depending on the outcome of the AUGMENT study, our valuation could increase by 60%. We currently assign no value to AUGMENT in ex-US markets or OvaTure, so these represent pure upside.

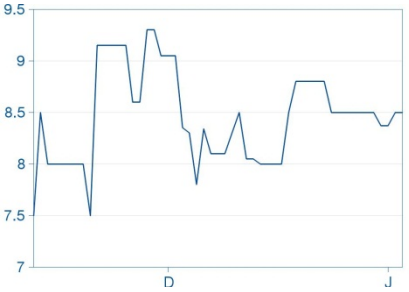
OvaScience is a research client of Edison Investment Research Limited

7 January 2013

Price	$8.50
Market cap	$121m

Shares in issue	14.3m
Free float	53%
Code	OVSC
Primary exchange	OTC

Share price performance



%	1m	3m	12m
Abs	1.5	N/A	N/A
Rel (local)	1.0	N/A	N/A
52-week high/low		N/A	N/A

Business description

OvaScience is a US-based life sciences company focused on developing and commercialising new treatments for infertility. The company's products (AUGMENT, OvaTure) are based on the discovery of egg precursor cells in ovaries. Both products are designed to improve *in* vitro fertilisation.

Next events

OvaTure Preclinical data	H114
AUGMENT study results	H214

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Investment summary

Company description: Harnessing stem cells to improve IVF

OvaScience is a US life sciences company developing novel treatments for female infertility. Its two product candidates – AUGMENT and OvaTure – are designed to enhance the current IVF process. The company's novel, patented technology is based on the recent scientific discovery of germline stem cells (EggPC) in human ovaries. Lead candidate, AUGMENT, is a process of injecting a woman's own EggPC mitochondria into her eggs during IVF to improve the success rate. Positive results from the AUGMENT study (started Q412, results H214) could trigger a US commercial launch in H214. Preclinical candidate, OvaTure, uses EggPC to create mature eggs for use in IVF. OvaScience was formed in April 2011 and, since inception, has raised $45.3m (net) in three private rounds. In November 2012, OvaScience began trading 7.6m shares on the OTC Market. An additional 6.6m shares will become eligible for sale over the 2013-15 timeframe once various lock-up agreements expire.

Exhibit 1: OvaScience R&D pipeline

Product	Description	Stage	Comments
AUGMENT	Improve egg quality using EggPC mitochondria	Clinical	40-patient AUGMENT study in 38-42yr old women with 2-5 prior IVF cycle failures started in Q412 (results mid-2014). Targeted US launch in H214.
OvaTure	Mature fertilisable eggs from EggPC	Preclinical	Preclinical proof-of-concept studies in progress, expected completion H114. Targeting start of human clinical trial in 2015 under IND.

Source: Edison Investment Research

Valuation: Risk-adjusted NPV of $146m

We value OvaScience at $146m, or $10.20 per share, based on a risk-adjusted NPV analysis, using a 12.5% discount rate. Our rNPV model, which includes AUGMENT and projected end-2013 net cash, represents upside to OvaScience's current market capitalisation of $121m and $8.50 share price. We value AUGMENT using prudent assumptions on the probability of success, launch date, pricing, commercialisation and market penetration. The investment case is subject to higher than normal risks (single clinical-stage product, regulatory), but this highlights the significant upside associated with a positive outcome in the AUGMENT study. Depending on these results, our valuation could increase by 60%. We place no value on AUGMENT in ex-US markets or OvaTure, so these represent pure upside.

Sensitivities: AUGMENT's clinical and regulatory risks

OvaScience is subject to the risks normally associated with biotech company development, including the possibility of unfavourable outcomes in clinical trials and the success of competitors. Because of its lack of diversification, there is particularly high sensitivity to the outcome of the AUGMENT study – negative data could represent a significant setback. Regulatory risk represents another key sensitivity. The FDA may decide to regulate AUGMENT as a new drug/biologic and require further clinical studies. This could substantially increase development costs and timelines and may require additional capital.

Financials: Cash runway into late 2014

OvaScience ended Q312 with cash of $35.1m. Our model, in line with company guidance, projects that OvaScience has sufficient cash to complete the AUGMENT study and fund the potential US commercial launch in H214. Of note, our model does not assume any revenue (upfront/milestones) from potential future licensing deals on AUGMENT (ex-US) or OvaTure.

Outlook: On fertile ground

OvaScience's near-term investment case effectively rests on the successful development and commercialisation of AUGMENT, its novel therapy to rejuvenate a woman's eggs and improve the success rate of IVF. The proprietary technology underpinning AUGMENT and preclinical candidate OvaTure is based on the discovery of egg-producing stem cells (EggPC) in human ovaries. The AUGMENT study in US women aged 38-42 failing two or more IVF cycles started in Q412, will readout in H214 and (if positive) could lead to a US commercial launch in H214. Provided AUGMENT shows a substantial improvement in IVF success rates, is safe and retains its lower-risk regulatory status, peak sales potential in the US could be $160m/year. We value OvaScience at $146m, or $10.20 per share.

Exhibit 2: OvaScience R&D pipeline

Programme	AUGMENT	OvaTure
Stage	Clinical study	Preclinical
Therapeutic aim	Improve egg quality (and hence IVF success) by injecting mitochondria from woman's own EggPC into her egg.	Creation of mature fertilisable eggs from a woman's own EggPC.
Study details	AUGMENT study in 38-42 yr old women failing 2-5 cycles of IVF.	Preclinical proof-of-concept studies in progress.
Timeline	AUGMENT Study initiated in Q412, headline results in H214, target commercial launch in H214.	Initiate preclinical development in H212, complete preclinical studies in H114. Initiate human clinical trial in 2015.
Patent protection	Five patent families. Patents granted (and pending) to May 2025. Additional patent applications, which would expire April-June 2032.	Five patent families. Patents granted (and pending) to May 2025. Additional patent applications, which would expire April-June 2032.
Potential regulatory pathway	361 HCT/P: a lower-risk human cell and tissue product (HCT/P) pathway.	New Biologics Licence Application (BLA) process.

Source: Company documents, Edison Investment Research

Harnessing egg-producing stem cells

Landmark discovery of germline stem cells

OvaScience's product candidates – AUGMENT and OvaTure – are based on the ground-breaking scientific discovery of germline stem cells (EggPC) in human ovaries. Traditional scientific dogma holds that women are born with a fixed number of eggs (oocytes), which are progressively depleted throughout life. For over 60 years, it was assumed that adult women could not replenish their egg supply through germ-cell renewal. This view has, however, been challenged by the recent discovery of EggPC in the ovaries of adult mice and humans – this cutting-edge science led to the formation of OvaScience.

In 2004, Dr Jonathan Tilly (co-founder of OvaScience) announced the discovery of EggPC in the ovaries of adult mice.[1] In a series of experiments, Dr Tilly concluded that mouse EggPC could generate new eggs in a similar way to sperm production in the male testes. Provisional EggPC were first identified in mouse ovaries using an antibody that binds to mouse vasa homolog (MVH), a protein found on germline stem cells. Normal mouse ovaries were then implanted into transgenic mice that expressed green fluorescent protein (GFP) in their cells. After several weeks, the grafted ovaries were collected and processed for GFP expression. These ovaries contained GFP positive eggs, indicating that transgenic germ cells had infiltrated the grafted tissue and initiated egg production.

1 Johnson J et al, Nature 2004; 428:145-150

Dr Tilly's findings were controversial with many reproductive and stem cell experts sceptical that such egg-producing stem cells existed. However, independent studies confirmed the existence of EggPC in adult mouse ovaries: EggPC could be cultured in the laboratory (in vitro) for months and spontaneously generate what appeared to be immature eggs.[2] Moreover, EggPC could generate mature eggs in female mice (in vivo) and produce offspring.[3] Transplantation studies showed that EggPC injected into infertile mice could differentiate into mature eggs that were ovulated, fertilised and produced viable offspring. In another study, EggPC from elderly mice could restart egg production when transplanted into younger adults.[4] Finally, adult mouse ovaries could be stimulated to produce new eggs by small molecule drugs and unidentified blood factors.

In early 2012, Dr Tilly reported the existence of EggPC in the ovaries of reproductive-aged women.[5] He also showed, for the first time, that eggs from EggPCs were fertilisable. These experiments employed a more selective method, called fluorescence-activated cell sorting (FACS), to isolate and purify EggPC from mouse and human ovaries. The FACS approach tagged EggPC with a fluorescently labelled antibody to MVH and collected them one-by-one. The application of FACS to human ovaries (harvested from six women aged 22 to 33) identified cells with a gene expression profile consistent with EggPC. Results of subsequent in vitro and in vivo studies provided further support that these were germline stem cells:

- Human EggPC were grown in cell culture (in vitro) and spontaneously generated immature human eggs (as determined by appearance/structure, gene expression and haploid status); and
- Human EggPC were then labelled with GFP to make them traceable, injected into human ovarian tissue and transplanted into female mice. After one to two weeks, the transplanted EggPC formed green-glowing cells that looked like human eggs and bore the genetic hallmark of this cell type.

Role of EggPC subject to ongoing debate

Taken together, we believe these data provide convincing evidence for the existence of human EggPC and, moreover, the potential to create new eggs. However, given the cutting edge nature of Dr Tilly's discoveries, there is (understandably) ongoing debate over the role of human EggPC in female reproduction. In particular, it remains unknown whether human EggPC can (1) form new eggs naturally in the body, (2) be matured in the laboratory into fertilisable human eggs, and (3) generate a normal early embryo once fertilised.

Provided these key questions are resolved, human EggPC might improve the success of assisted reproduction (IVF) by:

- Providing a source of fresh cellular components to rejuvenate a woman's existing eggs.
- Generating new eggs for women with a compromised egg supply. This would include cancer patients who have undergone sterilising chemotherapy, women with premature menopause, or older women wishing to conceive.
- Allowing scientists to run in vitro screens on EggPC to determine if hormones or drugs can stimulate the cells to produce fertilisable eggs.

Exclusive licence to proprietary EggPC technology

OvaScience's broad intellectual property portfolio should protect the AUGMENT procedure until at least 2025 and, potentially, through to 2032. The company has an exclusive licence from the Massachusetts General Hospital (MGH) to an issued US composition-of-matter patent (expiring May

2 Pacchiarotti et al, Differentiation 2010, 79(3):159-170
3 Zou et al, Nat Cell Biol 2009;11(5):631-6
4 Niikura et al, Aging 2009;1:971-978
5 White et al, Nature Medicine 2012; 18:413-421

2025) and various US/EU/international patent applications for methods of identifying and purifying human EggPC, compositions comprising EggPC and methods of using EggPC to treat infertility and related disorders. There are five patent families, which include patents granted (and pending) that expire in 2025, and additional patent applications that would expire in 2032.

The issued COM patent includes claims directed to isolated non-embryonic stem cells that express the protein markers characteristic of female EggPC – this covers therapeutic products containing EggPC (OvaTure, AUGMENT). Two families of patent applications (autologous germline mitochondrial energy transfer, enhancing bioenergetic status of eggs and EggPC) should provide additional protection for the AUGMENT procedure. Finally, there are two pending patent families that could provide an alternative method of obtaining EggPC from blood and bone marrow.

Exhibit 3: OvaScience's intellectual property portfolio

Patent family	Territory	Status	Expiry
Methods of isolating female EggPC, various uses for female EggPC including methods for IVF, egg production, treating infertility and restoring egg production	US, Europe	US – issued EU – pending	US – May 2025 EU – May 2025
Methods and compositions for producing female EggPC from stem cells derived from bone marrow	US	Pending	US – May 2025
Methods and compositions for producing female EggPC from stem cells derived from peripheral blood (alternative method of obtaining EggPC)	US	Pending	US – May 2025
Methods and compositions for autologous germline mitochondrial energy transfer	US, International	US – pending Intl – pending	US – April 2032 Intl – April 2032
Methods and compositions for enhancing the bioenergetic status in female EggPC	US, International	US – pending Intl – pending	US – June 2032 Intl – June 2032

Source: OvaScience Form S-1

Terms of licensing agreement with MGH

In June 2011, OvaScience acquired exclusive, worldwide rights to specific patents owned by MGH and non-exclusive rights to know-how relating to the licensed patents. In September 2011, the agreement was amended to include an additional patent owned by Harvard, for which MGH was able to grant licence rights. The licence under the MGH-owned patents and know-how is for human female fertility and the licence under the Harvard-owned patents is for human female fertility treatments.

Under the agreement, OvaScience paid MGH an upfront fee of $335k, with MGH also eligible for annual licence fees (creditable against future royalties), annual maintenance fees (starts 2013, estimated annual cost $62k), development and commercial milestones (up to $10.5m) and royalties on net sales (we assume 3%). In addition, MGH will receive $1m in connection with either the first underwritten IPO or a change of control.

Infertility background

Exhibit 4: Infertility background

What is infertility?	Infertility is the failure to achieve pregnancy after 12 consecutive months (or six months for women over 35yrs) of regular unprotected intercourse.
Incidence/ prevalence	One in six couples globally experience some form of infertility problem at least once during their reproductive life. Worldwide prevalence of infertility among women aged 20-44 is around 9%. In the US an estimated 7.4 million women aged 15-44 have used infertility services, 6.7 million (11%) have impaired fertility, and 1.5 million (6%) married women are infertile.
What are the causes of infertility?	The process of natural conception has many stages and failure in any one is a potential cause of infertility. Overall 20-30% of infertility cases are due to problem in partners (male and female), 20-30% due to male factors, 20-35% due to female factors, and 10-20% no cause found. Leading causes of infertility in women include: 1) diminished ovarian reserve – ability of ovary to produce normal quality eggs is reduced due to advanced age, medical or surgical causes; 2) ovulatory dysfunction – ovaries are not producing eggs normally (ie polycystic ovaries, ovarian cysts); 3) tubal factors – fallopian tubes are blocked or damaged; 4) endometriosis – uterine lining tissue in abnormal locations; and 5) unexplained causes. In 2010, the leading causes of infertility among US couples receiving ART were: 18% multiple female and male factors (both partners infertile), 17% male-only factors, 15% diminished ovarian reserve, 12% unknown factors, 7% ovulatory dysfunction and 7% tubal factors.
Current treatments – assisted reproductive technology (ART)	While there are various definitions of ART, the US CDC includes all fertility treatments in which both eggs and sperm are handled. In general, ART procedures involve surgically removing eggs from a woman's ovaries, combining them with sperm in the lab and returning them to the woman's body or donating them to another woman. An ART procedure includes several steps and is typically referred to as a treatment cycle. ART does not include treatments in which only sperm are handled (i.e. intrauterine insemination) or when a woman takes drugs only to stimulate egg production. Types of ART include: IVF – extracting a woman's eggs, fertilising them in the lab, then transferring the embryo into the woman's uterus through the cervix. The majority of IVF procedures use intracytoplasmic sperm injection (ICSI) where a single sperm is injected directly into the egg. In addition, ART is categorised according to whether a woman's own eggs (nondonor) or another woman's (donor) and whether the embryos were newly fertilised (fresh) or previously fertilised, frozen and thawed (frozen).
What is an ART cycle?	An ART cycle consists of several steps over a number of weeks. It starts when a woman takes drugs to stimulate the ovaries to develop eggs or, if drugs are not used, when the woman's ovaries are monitored (ultrasound, blood tests) for natural egg production. The cycle progresses to egg retrieval where eggs are surgically collected from a woman's ovaries. Retrieved eggs are combined with sperm in the lab, fertilised, then one or more embryos are selected for transfer into the uterus via the cervix (IVF) or sometimes into fallopian tubes (GIFT, ZIFT). If the embryo implants in the uterus it may progress to pregnancy, which could become a live birth.
What is the most common type of ART?	Around 1.5m ART cycles are performed each year worldwide, with an estimated 350,000 babies born. IVF is by far the most common ART procedure in the US and globally. In the US, IVF accounted for 99% of the 147,000 ART cycles undertaken in 443 US clinics during 2010, with ICSI used in 66% of procedures. In addition, 70% of these ART cycles used fresh nondonor eggs, followed by 18% frozen nondonor and 12% fresh or frozen donor eggs. In Europe, 537,000 ART cycles were reported from 33 countries during 2009. The leading European countries were France (75,000), Germany (68,000), Spain (54,000) and UK (54,000).
Who uses ART?	The most active countries are the US and Japan. In the US and globally, women are having children late in life; however, ovarian reserve and egg quality diminishes with increasing age. A woman's chances of conceiving within one year decrease from 75% at age 30 to 44% at age 40. Thus, increasing age is one of most common causes of infertility and most ART treatments take place in women aged 30-39. In the US, 66% of nondonor ART procedures in 2009 were in women aged 30-39, with 22% in women over 40.
What is the success rate for ART?	Global data for 2007 suggested that 22-27% of ART cycles resulted in live births. US success rates have modestly increased over last decade but remain relatively low: 31% of all ART cycles in 2009 resulted in live births. Patients using nondonor eggs have lower success rates than use of donor eggs. According to the CDC, in 2009, 30% of fresh nondonor ART cycles resulted in live births, contrasting with 55% using fresh donor eggs. The success rate for IVF with nondonor eggs declines rapidly with increasing age, while success rates with donor eggs remains relatively flat. According to CDC, in 2010, the success rate of IVF with fresh nondonor eggs declined from 42% in women aged <35 to only 1% in women >44. In Europe in 2009, the mean pregnancy rate per embryo transfer was 33% after conventional IVF, 32% after IVF with ICSI, 23% after frozen embryo transfer, and 42% after egg donation.

Source: Edison Investment Research, CDC, ESHRE, SART

AUGMENT targets growing unmet need

OvaScience's AUGMENT is designed to improve the success rate of IVF, an area with relatively limited advances since its introduction in the late 1970s. Current 'state of the art' IVF still has significant shortcomings (modest success, requires hormonal hyperstimulation, high out-of-pocket cost) and results in healthy live births in less than a third of women. AUGMENT will initially target infertile women with the greatest unmet need – women requiring donor eggs and those aged >35 failing multiple IVF cycles. Success rates for these women are very low, declining from around 22% at 38-40 years to 4% above age 43. In 2010, we estimate that US women aged over 35 received 85,000 cycles of IVF. With 25% of individuals requiring more than two cycles, this translates into an initial target market for AUGMENT of 25,000 women. Expanding the use of AUGMENT into women with just one prior failed cycle would increase this market opportunity to 35,000.

Infertility affects 11% of US childbearing women

Infertility is the failure to achieve pregnancy after 12 consecutive months (or six months for women over 35) of regular unprotected intercourse. Pregnancy is a multi-stage process, namely 1) a woman's body releases an egg from her ovaries (ovulation), 2) the egg travels through the fallopian tube to the uterus (womb), 3) a man's sperm fertilises the egg and 4) the fertilised egg attaches inside the uterus (implantation). Infertility can arise if there are problems with any of these steps. Broadly, a third of infertility cases are female-specific, a third due to male factors, and the rest a combination of factors or unknown problems.

Infertility is a common problem in the US and worldwide. An estimated one in six couples globally experience infertility problems during their lives, with the current prevalence of infertility estimated at around 9% for women aged 20-44.[6] In the US, around 7.4 million (12%) women of childbearing age have used an infertility service, 6.7 million (11%) have impaired fertility and an estimated 1.5 million (6%) married women are infertile.[7] Around 1.2 million women seek infertility treatment annually in the US.[8] Although 12% of US women access infertility services during their lifetime, only 1-2% receive IVF.

Increasing age is a leading cause of infertility

Increasing age in the female partner is one of the most common causes of infertility. In the US and globally, an increasing number of women are delaying childbearing until their late 30s and 40s. However, a woman's chances of conceiving naturally decline with increasing age from approximately 75% at age 30 to 44% by age 40. Advancing age is associated with declining capacity of the ovary to provide healthy eggs that are capable of fertilisation. Unfortunately, as discussed below, the success of infertility therapy using a woman's own eggs also declines significantly with increasing maternal age.

IVF is the most common type of ART

There are broadly two categories of infertility therapies – those that handle both eggs and sperm (ART), and those that do not handle eggs (fertility drugs, intrauterine insemination). Since the birth of Louise Brown, the first IVF baby, over 30 years ago, it is estimated that over 3.5 million children have been born worldwide following ART treatment. ART-conceived infants account for 1% of US births annually and up to 4% in some European countries.[9] IVF is by far the most common type of ART, accounting for over 99% of procedures in the US. An IVF procedure involves several steps over a two-week period, which is referred to as a treatment cycle. A typical IVF cycle begins by stimulating a woman's

6 ESHRE ART fact sheet
7 CDC, Key Statistics from National Survey of Family Growth (2006-2010)
8 CDC, Fertility, Family Planning, and Reproductive Health of US Women (2002)
9 ESHRE, Hum Reprod 2009;24:1267-1287

egg production with fertility drugs, then surgically extracting the eggs, fertilising the eggs with sperm in the laboratory (in vitro), and transferring the resulting embryo(s) into the woman's uterus. IVF uses either a woman's own eggs (nondonor) or donated eggs (donor), which are either newly fertilised (fresh) or previously fertilised and frozen (frozen). Clearly, couples seeking to preserve a genetic match must use nondonor eggs and sperm. In 2009, the vast majority of US women younger than 35 (97%) used their own eggs, whereas most women older than 44 (73%) received donor eggs.

The majority of IVF procedures use ICSI

For many IVF procedures, the egg is fertilised by directly injecting a single sperm using a small needle. This approach, called ICSI (intracytoplasmic sperm injection), was originally developed to treat male infertility but is now widely used in IVF. In the US, ICSI accounts for two-thirds of all IVF procedures. While the use of ICSI is accepted and widespread, there has recently been some controversy surrounding this approach. An Australian registry study suggested that ICSI is associated with a small but significant increased risk of birth defects (9.9%) versus natural conception (5.8%).[10] However, this study has been criticised for the comparator groups used, lack of detail on reasons for ICSI, and possibility of residual confounding. The continued use (and safety) of ICSI is highly relevant to OvaScience's lead programme, AUGMENT, which is delivered with ICSI (see below). Thus, the potential commercial success of AUGMENT hinges on the continued use and acceptance of ICSI.

Later childbearing is driving growth in IVF

Approximately 1.5m IVF cycles are performed across 3,000 clinics worldwide each year, including an estimated 540,000 procedures in Europe and 150,000 in the US.[11] The number of IVF cycles in many developed countries has grown by 5-10% per year over the last five to six years. Based on SARTS data, we estimate that IVF use in the US has grown by 4% CAGR over 2005-10. The increasing use of IVF reflects the trend of later childbearing and its associated impact on age-related fertility, rising rates of obesity, some sexually transmitted diseases and increasing acceptance of reproductive technologies.

IVF dominates the $4bn US infertility market

The US market for infertility services, encompassing fertility medications ($1.5bn) and ART procedures ($2.5bn), was estimated at $4bn in 2008[12]. IVF accounted for 99% of the 147,000 ART cycles performed in 443 US clinics during 2010, with ICSI used in 66% of cases. There is only one corporate chain of IVF clinics in the US, Integramed, with 40 practices nationwide, and most IVF programmes are run by small physician practices or university hospitals. The average age of women using IVF services is mid-thirties (36 in 2009) and over 60% of procedures are undertaken in women over 35. In 2009, IVF resulted in 46,000 live births in the US (delivery of one or more infants) and 60,000 infants.

Despite its high cost, time requirements, risks and relatively limited success, there is growing use of IVF by US women: an increase from 112k procedures in 2003 to nearly 150k in 2010. This growth in demand is driven primarily the over six million infertile women, whose ranks are being swelled by women delaying childbirth.

IVF is typically an out-of-pocket expense for US couples – there is virtually no government subsidisation and limited private insurance coverage. As such, we expect that US patients will pay out of pocket for AUGMENT in addition to the IVF procedure. The average cost of a single IVF cycle in the US (in 2006 dollars) has been estimated at $12.5k.[13] OvaScience estimates that the average cost per cycle is $16k for nondonor and $26k for donor eggs. Since patients frequently require more than one

10 Davies et al, NEJM 2012;366:1803-1813

11 SART, National Data Summary 2010

12 Marketdata Enterprises, 2009

13 Chambers G, Fertil Steril 2009;91(6):2281-94

cycle, the total cost of IVF treatment can be significantly higher. Median total treatment costs (ie total number of IVF cycles per patient) were recently estimated at $24k and $38k for nondonor and donor IVF groups respectively.[14] The costs per successful outcome (live birth), which factors in a 30% success rate, were even higher at $61k and $72k respectively. The high cost of IVF is, unsurprisingly, a major driver of use – the US undertakes the highest number of IVF procedures annually, but has one of the lowest utilisation rates of any developed country. Given that around one-half of couples do not seek medical help for infertility, there is potential high unmet demand for IVF therapy.

AUGMENT initially targets up to 35,000 infertile US women

OvaScience's first product, AUGMENT, will initially target US women requiring donor eggs and those aged >35 failing two or more IVF cycles. According to SART, US women aged >35 received c 70,000 cycles of nondonor IVF in 2010.[15] With published data suggesting that 25% of women require more than two cycles, this equates to around 10,000 individuals.[16] In addition, 15,000 cycles of donor IVF were undertaken in the US during 2010, with the vast majority likely to have been undertaken in older women failing multiple nondonor cycles. Taken together, this suggests an initial target population for AUGMENT of 25,000 infertile US women. Potential further expansion into women over 35yrs failing just one IVF cycle could increase the target market to 35,000.

IVF still has significant limitations

Despite the growing use of IVF worldwide, the procedure is limited by its low success rates and, if unsubsidised (as in the US), can be a significant economic burden to patients (Exhibit 5).

Exhibit 5: Shortcomings of IVF

Key limitations of IVF	Detail	How AUGMENT might address shortcoming?
Relatively low success rates	Only 31% of IVF cycles resulted in live births in the US during 2009. The success rate for women using their own eggs (nondonor) is substantially lower (30%) than patients receiving donor eggs (55%). Most notably, the success of nondonor IVF declines rapidly with advancing age (42% for women <35yrs vs 1% for >44yrs) while success for women >35 are flat with donor eggs (c 50%).	Improving egg quality may increase the proportion of healthy pregnancies and live births.
Requirement for multiple cycles	A substantial number of women require more than one IVF cycle to achieve pregnancy and live birth. This is physically and emotionally draining, magnifies the risks associated with the IVF procedure, and significantly increases the cost of treatment. A recent Massachusetts registry study revealed 14,300 women who averaged 1.9 IVF cycles – 50% of patients received one cycle, 25% two cycles, 13% three cycles and 12% four or more. In this study the success of IVF (live births) declined with each successive cycle from 30% on the first to 23% by the fifth. Reflecting this, the cumulative live-birth rate increased from 30% (cycle 1) to a plateau of around 54% (cycle 5 onwards). The cumulative success rate for nondonor IVF declined steadily from 60% for women <35 to only 9% for women >43.	Increasing the success rate for an IVF cycle would reduce the number of cycles required to achieve a successful birth.
High treatment cost	Infertility treatment in the US is usually paid for out of pocket. The cost of IVF varies substantially between countries, with the US standing out as most expensive. Moreover, the cost within each country varies according to the treating centre/physician, use of ICSI, cost of medications, and egg type (nondonor, donor). The cost of a single IVF cycle in the US was estimated at $12.5k in 2006. OvaScience estimates that the current cost per cycle for nondonor and donor IVF is $16k and $26k respectively. Median per-person (total treatment) costs were recently estimated at $24k and $38k for nondonor and donor IVF, respectively. Estimated cost per successful outcome (live birth) is even higher at $61k and $72k, respectively, reflecting that only 30% of women achieve live birth. The provision of IVF in the US contrasts with most European countries, which funds a limited number of cycles based on female age, and Australia, which has unrestricted reimbursement with co-payments. The cost of one IVF cycle in the EU ranges from around $3k to $6.2k.	Reducing the number of IVF cycles required for a successful outcome, as well as the incidence of multiple births, could lower both the direct and indirect costs of treatment.
High incidence of multiple births	While it is common practice in IVF to transfer several embryos, in an attempt to increase the success rate, it also increases the rate of multiple births. Multiple gestations can increase the risks to mother and babies, including preterm birth and low birth rate. In the US in 2009, the multiple birth rate was 31% for IVF pregnancies using nondonor eggs, compared to only 3% in natural pregnancies. The costs of caring for multiple-birth ART infants can be substantial, reflecting the underlying morbidity associated with such pregnancies.	Higher-quality eggs could lead to the transfer of fewer embryos per IVF cycle and, as such, reduce the rate of multiple births.

Source: Edison Investment Research

14 Katz et al, Fertil Steril 2011;95(3):915-921

15 SART US National Data Summary 2010

16 Stern et al, Fertil Steril 2010;94(4):1334-40

AUGMENT: Rejuvenating eggs to improve IVF success

OvaScience's lead programme, AUGMENT (AUtologous Germline Mitochondrial ENergy Transfer), aims to improve the success rate of IVF in women by rejuvenating their eggs. If successful, this approach could eliminate the need for donor eggs and allow women to have their own biological children. The AUGMENT procedure extracts 'fresh' mitochondria from a woman's own EggPC and injects them into her egg during the IVF procedure. This is based on scientific evidence that mitochondria are central to egg quality, providing the energy for successful fertilisation and embryo development. However, the number and quality of mitochondria in eggs declines with increasing maternal age, which is likely to form the basis of sharply declining fertility and IVF success rates in older women. With the increasing numbers of women delaying childbearing for professional reasons, demographic trends support the need for new approaches to improve infertility therapy.

Backed by positive preclinical results and encouraging human proof-of-concept data (cytoplasmic and somatic mitochondria transfer), OvaScience is undertaking the AUGMENT study in older women (38-42yrs) who have failed multiple (two to five) cycles of IVF. The study commenced in Q412, will deliver final results (live birth rates) in H214, and (if positive) could lead to a US commercial launch shortly thereafter. Provided AUGMENT is safe, shows clinically relevant efficacy and retains its lower-risk regulatory status, we see the product delivering peak US sales of $160m/year. This based on prudent assumptions of AUGMENT's marketed indication (women requiring donor eggs and/or aged >35 failing at least two IVF cycles), probability of success (60%), launch date (H214), pricing ($15,000 per procedure), commercialisation (US only) and peak market penetration (25% share of both the donor egg market and women aged >35). We view a 60% risk-adjustment as adequately reflecting the clinical and regulatory risks associated with the AUGMENT procedure.

Mitochondria: The cell's powerhouse

Mitochondria are the structures within mammalian cells responsible for energy production. They are cellular power plants because they combine glucose with oxygen to produce adenosine triphosphate (ATP), which is the cell's primary energy source. Mitochondria also have a role in cell signalling, differentiation and control of the cell cycle and growth.[17] Importantly, mitochondria contain a small amount of genetic material (mitochondrial DNA, mtDNA), inherited solely from the mother, that encodes key proteins responsible for normal mitochondrial function. Unlike nuclear DNA, which is inherited 50/50 from mother and father, mtDNA is inherited solely from the mother.

Mitochondria are critical for healthy eggs and embryos

Mitochondria are the primary source of energy in mature, fertilisable eggs and the early embryo. It has been shown that eggs with sufficient mitochondria, and therefore capacity to generate ATP, develop normally during subsequent embryo growth.[18] There is a strong association between the number of mitochondria in eggs (measured by mtDNA count) and successful fertilisation. Specifically, good-quality eggs have been shown to contain significantly higher numbers of mitochondria, and hence, higher rates of fertilisation compared to poor-quality eggs.[19] It appears that eggs require at least 100,000 functioning mitochondria to be successfully fertilised and develop into a healthy embryo.[20]

17 McBride et al, Curr Biol 2006;16(14):551-60

18 Hua et al, Cloning and Stem Cells 2007;9(2):237-246

19 Santos et al, Fertil Steril 2006;85:584-591

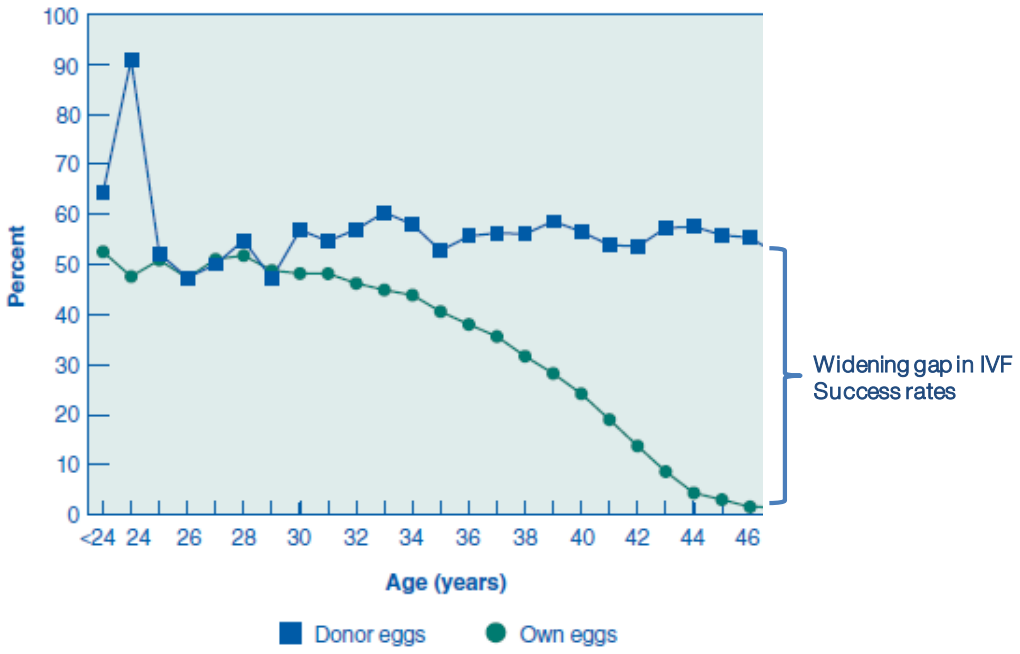
20 Wang et al, Journal of Zhejiang University 2009;10:483-492

Older women's eggs contain fewer mitochondria

A woman's eggs contain a fixed number of mitochondria, which are divided up among daughter cells after fertilisation. No new mitochondria are synthesised until the embryo is at least five or six days old (blastocyst phase), which ensures embryonic cells contain only high-quality mitochondria inherited from the mother.[21] During initial embryo development, the number of mitochondria in each cell is diluted by ongoing cell division and a lack of mitochondrial production. Thus, if the mother's egg already contains a low number of mitochondria, or they are dysfunctional (faulty), then energy production will be compromised – this could negatively affect fertilisation, implantation and embryo development.

Eggs in older women contain fewer mitochondria and more dysfunctional mitochondria. The latter arises from genetic (mtDNA) mutations that result in faulty proteins required for ATP production.[22] These observations might explain the "gap" in success rates for nondonor versus donor IVF in older women – energy production in a woman's own eggs (nondonor) declines as she ages, whereas young donor eggs have an ample supply of functioning mitochondria (Exhibit 6).

Exhibit 6: Success of nondonor IVF declines with age



Source: US CDC 2009

It is hypothesised that adding mitochondria to eggs at fertilisation might provide the critical energy boost for initial embryo development, ie the short period before the embryo starts generating its own mitochondria.[23]

Preclinical studies: Mitochondria and cytoplasmic transfer effective in multiple species

Preclinical studies have shown that adding isolated mitochondria or cytoplasm (containing mitochondria) to eggs increases their energy (ATP) levels, likelihood of fertilisation and rates of healthy

21 Wong C et al, Nature Biotechnology 2010;28:1115-1121
22 Jacobs et al, Molecular Human Reproduction 2007;13:149-154
23 Nagai et al, Hum Cell 2004;17(4):195-201

live birth. Supportive data has been generated in various species, including mice, rabbits, pigs and cows (Exhibit 7).

Exhibit 7: Supportive preclinical data for cytoplasmic and mitochondrial transfer

Species	Cyto or Mito transfer	Healthy egg	Higher fertilisation rate	Healthy embryo	Healthy live births	Key study detail	Reference
Mouse	Cyto, Mito	Yes	Yes	Yes	Yes	Mitochondrial concentrates injected into mouse embryos resulted in increase in progression to blastocyst stage with no untoward effects on offspring.	Yi et al, J Assist Reprod Genet 2007;24:445-459
Rabbit	Cyto	Yes	Yes	Yes	Not reported	Transfer of maternal cytoplasm into high-quality egg did not affect survival of egg, fertilisation rate or embryo growth/development. However, donor cytoplasm decreased the number of fertilised eggs reaching embryo stage.	Li et al, Electronic Journal of Biology 2005;1:6-8
Pig	Cyto, Mito	Yes	Yes	Yes	Not reported	Supplementing eggs with mitochondria from maternal relatives showed a significant improvement in fertilisation outcomes following IVF with ICSI. This suggests that mitochondrial number is critical for fertilisation and embryo growth	El Shourbagy et al, Reproduction 2006;131(2):233-245
Cow	Cyto, Mito	Yes	Yes	Yes	Yes (cyto)	Cytoplasm (containing mitochondria) from a normal egg was injected into a poor-quality egg (containing chemically-damaged mitochondria) and fertilised. This resulted in normal egg development, fertilisation and birth of healthy offspring.	Chiaratti et al, Reproductive BioMedicine 2011;22:172-183

Source: Edison Investment Research

In summary, mitochondrial transfer has been shown to improve egg quality and reproductive success in multiple species. In particular, no concerns were raised over the number of mitochondria transferred. However, the source and quality of the mitochondria is paramount: best results were achieved with mitochondria from an animal's own reproductive cells, while mitochondria from donor or somatic cells triggered suboptimal results and potential safety issues. Donor mitochondria contain mtDNA that is genetically different to the recipient's mitochondria, which results in a cell with two types of mtDNA (called heteroplasmy). This genetic mismatch can impair ATP production, egg and embryo health, and could trigger mitochondrial or metabolic diseases.[24]

Human studies: Mitochondria and cytoplasmic transfer improves IVF success rates

A number of clinical studies have evaluated cytoplasmic transfer in women with recurrent IVF failure. In these trials, cytoplasm from young donor eggs was injected into older women's eggs during the IVF/ICSI procedure. With the caveat that each study was small, combined results point to increased rates of fertilisation, pregnancy and live births: 12 live births (16 offspring) in the 30 women who had failed two to five IVF cycles.[25] However, one twin pregnancy included a case of Turner syndrome (incidence of 5.9%, top end of the 1-6% rate seen in normal population) and one child developed ADD (background incidence 0.2%). As noted above, there are real safety and ethical concerns with mixing DNA from three sources – mtDNA from donor cytoplasm, oocyte genomic DNA and mtDNA from the mother, and sperm genomic DNA from the father. As a consequence, the US FDA now requires an IND filling (ie full drug development programme) for cell therapies involving the transfer of third-party genetic material (including mtDNA).

24 Spikings et al, Hum Reprod Update 2006;12(4):401-15

25 Cohen et al 1997, 1998; Brenner et al, 2000; Barritt et al, 2000, 2001

A seminal study by Tzeng el al (2004) took mitochondria from a woman's own granulosa cells (GCs, ovarian cells surrounding oocytes) and injected them into her eggs during IVF/ICSI.[26] The use of autologous GCs resulted in a healthy live-birth rate of 27% and, importantly, avoided introducing third-party mtDNA. However, GCs contain the same 'old' mitochondria as those in the mother's eggs.

Exhibit 8: Clinical studies of mitochondrial transfer

Procedure	Mitochondria source	Cell type	Number of mitochondria transferred	Number of cycles	Live births	Offspring delivered	Implied live-birth success rate
Cytoplasmic transfer	Donor	Egg	Unknown	30	12	16	40%
Cytoplasmic transfer	Donor	Egg	Unknown	4	1	2	25%
Cytoplasmic transfer	Donor	Egg	Unknown	9	4	5	44%
Mitochondrial transfer	Autologous	Granulosa (somatic)	3000 (average)	71	20	27	28%

Source: Edison Investment Research

AUGMENT has advantages over historical approaches

Building on these studies, AUGMENT will isolate mitochondria from a woman's EggPC and inject them into her egg to improve egg quality. This contrasts with existing approaches that transferred mitochondria from donor eggs or somatic cells. As such, AUGMENT has three potential advantages:

- Autologous – using the woman's own mitochondria ensures that only her genetic material (mtDNA) is transferred in the egg. This should, in theory, avoid the safety, ethical and regulatory issues associated with the use of donor mitochondria.
- Pure – OvaScience's proprietary technology (FACS-based isolation, VASA antibody) provides highly purified EggPC with a single ovarian biopsy providing mitochondria for two/three IVF cycles.
- Fresh – Mitochondria from EggPC are 'fresh' with stable energy (ATP) production and mutation-free mtDNA.
- Accurate and reproducible – A mature human egg contains around 150-250k mitochondria, with poor quality (degenerate) eggs around 50-100k.[27,28] It appears that a healthy egg requires at least 100k mitochondria to successfully fertilise. The AUGMENT procedure will add a defined (undisclosed) number of EggPC mitochondria to older eggs, with the total mitochondrial count still well below the maximum (250k) total seen in normal eggs.

AUGMENT: Straightforward integration into IVF procedure

Exhibit 9 summarises how AUGMENT would integrate into the existing IVF procedure. The key difference versus standard IVF is the requirement for a core biopsy of ovarian tissue (3x3x1mm), which is obtained using laparoscopic (minimally invasive) surgery one month before the start of ovarian stimulation. Although laparoscopic biopsy requires a general anaesthetic, it is a common, day-case procedure often used to investigate female fertility; it is also associated with minimal risks of bleeding and/or infection. In addition, major IVF centres either have the capability to undertake laparoscopy or have established relationships with local hospitals. Thus, we do not see laparoscopy as a major impediment if AUGMENT shows a significant improvement in IVF success rates. Finally, in future it might be possible for ovarian biopsies to be undertaken transvaginally (well-established technique used to harvest eggs for IVF), which would be even less time consuming and invasive.

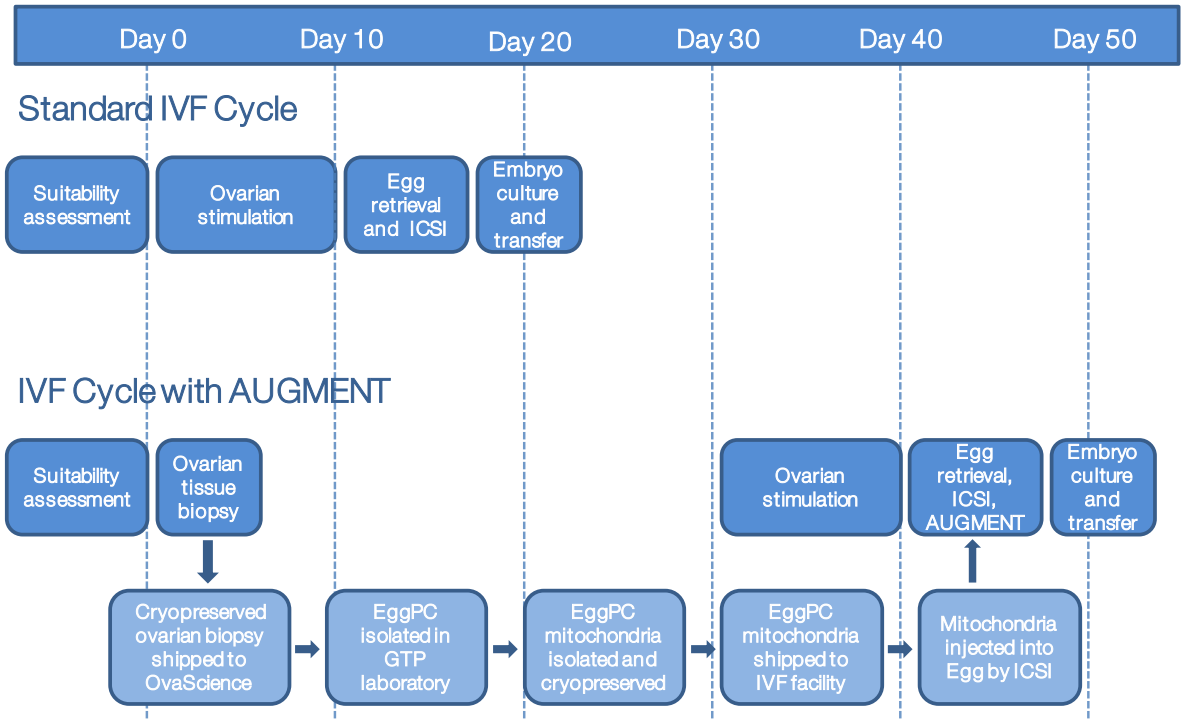
26 Tzeng et al, Fertility and Sterility 2004

27 Santos et al, Fertil Steril 2006; 85(3):584-91

28 May-Panloup et al, Hum Reprod 2005; 20(3):593-7

Ovarian biopsies are then cryopreserved (frozen) and shipped to OvaScience's cGTP-certified central laboratory, where the company's patented isolation process generates highly purified EggPC mitochondria in a reproducible and consistent manner.

Exhibit 9: AUGMENT adds several steps to standard IVF cycle



Source: Edison Investment Research

The frozen ovarian tissue is shipped to OvaScience's central laboratory, where it is thawed, washed and the EggPC isolated using the FACS procedure described earlier. For the AUGMENT study, purified EggPC are stored and frozen until the day of egg fertilisation with ICSI. At this time point, the EggPC are thawed and mitochondria isolated using a centrifuge. The mitochondria are then tested for their ability to make ATP and, once confirmed, placed in ICSI fertilisation buffer (the same solution used to inject sperm during ICSI). This mitochondrial solution is then transported to the IVF facility, where a tiny (ie picolitre) volume is injected during ICSI.

For the AUGMENT study, OvaScience will thaw the EggPC and isolate mitochondria on the day of the ICSI procedure. While this may be suitable for clinical study purposes (both IVF study centres are in the Boston area), the complexity of same-day EggPC thawing, mitochondrial isolation and ICSI could limit AUGMENT's commercial attractiveness. To address this, OvaScience plans to freeze the purified mitochondria, which would simplify the end-user process (physicians simply add mitochondria to ICSI buffer and inject), facilitate manufacturing scale-up and, importantly, reduce cost of goods. Encouragingly, the company has successfully completed initial experiments to support the use of frozen mitochondria.

OvaScience has contracted a third-party company, Agenus, to manufacture AUGMENT, from initial EggPC purification to diluting the mitochondria in ICSI solution. Importantly, Agenus is compliant with FDA regulations on the handling of human cells and tissues (current Good Tissue Practice, cGTP).

AUGMENT study: Results expected in H214

The US study for AUGMENT, which started in Q412, is expected to read-out in H214. The study protocol was approved by an independent Institutional Review Board, WIRB, and a university hospital academic review board. The open-label, non-randomised study at two IVF clinics close to Boston (one private, one university hospital) will recruit 40 women aged 38-42 years who have failed at two to five cycles of standard IVF. Women with obvious reasons for infertility (i.e. endometriosis, tubal factors) will be excluded. While there is no formal control arm, data from AUGMENT-treated patients will be compared to 40 similar patients who receive standard IVF at the same clinics. Each AUGMENT-treated patient will have only one embryo transferred during the IVF procedure.

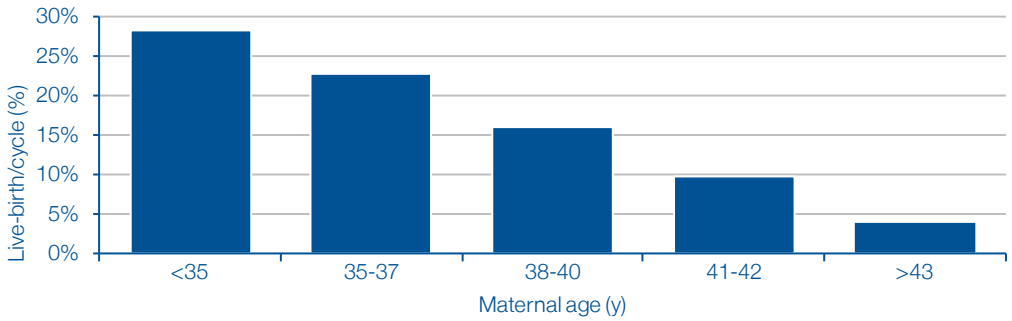
- Safety endpoints – this is the primary study objective and includes rates of adverse events, miscarriages, premature births, and congenital malformations.
- Efficacy endpoints – this includes embryo quality (at transfer), pregnancy rates (beta hCG levels, six- and 20-week ultrasounds), and, most importantly, healthy live birth rates. Provided the trial starts in Q412, final results (healthy live birth rates) are expected in H214.

The participating IVF clinics maintain databases that track their success rates. As such, results for AUGMENT will be compared to data for a similar group of women receiving standard IVF. This will include both clinic-specific data for IVF patients treated before the AUGMENT study (ie historic controls) as well as 40 matched patients receiving standard IVF during, but not part of, the study.

Based on published data, we expect the control group in the AUGMENT study to show a success (live birth) rate of around 14%. In 2010, IVF success rates for US women aged 38-40 and 41-42 were 22% and 13%, respectively.[29] However, these figures include all women, irrespective of whether they received one or many IVF cycles. Acknowledging this, data from a recent US cohort study of 14,300 women receiving IVF are more informative.[30] Results showed that 23% of women received three to five cycles, with a success rate of c 23% at this stage. In women aged 38-42 undergoing nondonor IVF, there were 214 births over 1,509 cycles, an implied success rate of 14%.

With the caveat that AUGMENT is primarily a safety study, we believe that a clinically meaningful increase in IVF success rates could be required to support initial commercial uptake. In our view, efficacy results showing at least a doubling of the birth rate (ie 25-30% vs 14% benchmark), equivalent to least 10 live births, would drive initial market uptake and support premium pricing.

Exhibit 10: Success rate for US women receiving three to four cycles of IVF



Source: Edison Investment Research (adapted from Stern et al, Fertil Steril 2010)

Depending on its outcome, OvaScience may extend the AUGMENT study or initiate a new trial to include additional sites and/or to expand the eligible population; the logical expansion would be into women aged >35 who have failed just one prior IVF cycle.

29 SART, National Data Summary 2010

30 Stern et al, Fertil Steril 2010;94(4):1334-40

Perceived regulatory pathway: A key sensitivity

OvaScience's near-term investment case effectively rests on the successful development and commercialisation of AUGMENT. As such, there is particularly high sensitivity to the outcome of the AUGMENT study and the product's perceived regulatory pathway. The company's business plan assumes that the US FDA will not regulate AUGMENT as a new drug or biologic requiring extensive clinical trials, premarket review and approval. Instead, OvaScience expects AUGMENT to be regulated as a 361 HCT/P, which applies to human cell- and tissue-based products (HCT/Ps) considered lower risk. Regulation under 361 HCT/P means AUGMENT is not subject to a full clinical trial programme, premarket review and approval. As such, the goal of the planned AUGMENT study is to provide adequate substantiation for any efficacy and safety claims made in future marketing materials.

Through a risk-based system introduced in 1997, the FDA regulates HCT/Ps under a two-tier framework. Higher-risk products are regulated as new drugs/biologics, being subject to thorough regulation by the FDA, while lower-risk products (361 HCT/Ps) are exempt from these requirements. The 361 HCT/P regulations are designed to prevent the spread of communicable diseases and require certain tissue manufacturing standards and controls, infectious disease testing and record keeping. OvaScience believes that AUGMENT meets all four criteria required for regulation under 361 HCT/P (Exhibit 11).

Exhibit 11: AUGMENT could be regulated under 361 HCT/P

Criteria for 361 HCT/P	Does AUGMENT meet criteria?
Minimally manipulated	AUGMENT is prepared using simple cell handling techniques to identify and isolate EggPC, and centrifugation of EggPC to separate out mitochondria. These steps do not alter the biological characteristics of the mitochondria.
Intended for homologous use as determined by product labelling and advertising	AUGMENT supplements a woman's pre-existing egg mitochondria with fresh mitochondria from her own EggPC.
Manufacture does not involve the combination of cells or tissues with another article	AUGMENT does not involve combining the HCT/P with any drugs, devices or synthetic materials. It does not require any culture. Mitochondria are diluted in standard ICSI buffer only.
It does not have a systemic effect and is not dependent on the metabolic activity of living cells for its primary function, or if it has such an effect, it is intended for autologous or allogenic use in close relatives or for reproductive use.	AUGMENT is intended for reproductive use and is autologous.

Source: Edison Investment Research

Recent years have seen acceleration in the development of novel HCT/Ps. As a result, there can be significant uncertainty surrounding the regulatory pathway (ie low or high risk) for such products. For example, the FDA recently argued that Regenerative Science's Regenexx Procedure (autologous stem cell therapy for joint/bone pain) was not a 361 HCT/P, as its cell culture and expansion involved more than "minimal manipulation". A US court agreed that Regenexx changes the biological characteristics of the cells. This case suggests that the FDA might take a narrow view of what constitutes minimal manipulation. It is important to note that AUGMENT, unlike Regenexx, does not require cell culture.

The Tissue Reference Group (TRG) is an advisory body within the FDA that provides formal opinions on whether a product will be regulated under 361 HCT/P. However, OvaScience has not (and is not) required to consult TRG based on its own conclusion that the product meets 361 HCT/P criteria. Without a formal TRG opinion, and uncertainty surrounding the terms "minimal manipulation" and "homologous", there is a risk that FDA will disagree with OvaScience. Moreover, given that AUGMENT is based on cutting-edge science that affects female reproduction, the FDA might wish to subject the product to a greater degree of scrutiny. If the FDA decides that AUGMENT is not a 361 HCT/P, OvaScience could be required to undertake an expensive and time-consuming clinical trial programme to secure marketing authorisation. This would significantly increase the size, costs and timelines of

clinical development – well above the 40-patient, $3.6-4.6m and 1.5-year timeframe for the current AUGMENT study. Finally, the FDA could make a decision at any time – during clinical development (potentially halting the study) or after commercial launch (which may lead to product withdrawal).

Commercialisation strategy: OvaScience to go it alone in US market

OvaScience intends to commercialise AUGMENT directly in the US market. In 2013, we expect initial commercial activities to be limited to ongoing conference presentations (ASRM, ESHRE), engagement with key US IVF centres (many are known to OvaScience), and interactions with leading US fertility experts. Provided final AUGMENT data are positive, the company would recruit a limited number of specialty sales people to initially target the highest volume IVF clinics (20 centres) performing c 30% of total IVF cycles annually. By 2015, a small team (up to 10) could expand this to 100 clinics (20% of US centres) that undertake c 70% of all IVF cycles.

Although IVF clinics are located throughout the US, the greatest concentration is in the eastern states (New Jersey, New York, Connecticut and Massachusetts). Moreover, we estimate that c 30% of IVF cycles annually are performed in 20 clinics, with 13 of these clustered along the east coast. Given that both OvaScience and Agenus (contract manufacturer for AUGMENT) are based in Massachusetts, this should ensure a smooth commercial launch and minimise logistical issues associated with the shipment of ovarian biopsies and AUGMENT.

Longer term, OvaScience believes that AUGMENT could be commercialised ex-US, either directly (EU countries with high-volume IVF centres, ie Belgium) or via partners (Asia, RoW, remaining EU territories). Expansion into these markets will hinge on the outcome of the AUGMENT study, a detailed market analysis (planned for 2013) and, most importantly, the success of any future US launch.

Relatively limited competition

Market uptake of an infertility therapy depends on its efficacy (healthy live birth rate), safety profile and overall cost to the patient. As such, the ability of AUGMENT to penetrate both US and international infertility markets will hinge on its ability to substantially improve IVF success rates while minimising risks and side effects. Moreover, if AUGMENT can reduce the number of IVF cycles, and hence overall costs, this would significantly enhance its competitive profile. A number of companies are developing products to address the shortcomings of IVF (Exhibit 12). Novocellus and Auxogyn are focused on identifying high-quality embryos for use in IVF, while Ovacyte is attempting to transform a woman's own ovarian surface epithelial cells (OSEs) into mature eggs. The latter, if successfully developed, would be a direct competitor to OvaScience's AUGMENT and OvaTure. However, while Ovacyte has an issued US patent, it appears that the technology is still in preclinical development and unpartnered.

Exhibit 12: Potential competition to AUGMENT

Company	Product	Stage	Detail
Novocellus	EmbryoSure	Retrospective clinical trial – targeted completion mid-2013, potential UK launch mid-2014	Embryo viability test, using culture media, to select high-quality embryos for IVF. Measures the turnover of natural amino acids by the embryo during its first 24 hrs of development. Done by analysing changes in amino acid content of medium in which embryo is cultured.
Auxogyn/Merck Serono	Early Embryo Viability Assessment System (Eeva)	EU – marketed in select countries (CE Mark) US – 510(k) application under FDA review	Software system to identify high-quality embryos. Proprietary software analyses embryo development against cell-division timing parameters, to identify the highest quality embryo within a group of embryos.
Ovacyte	Ovarian Surface Epithelial (OSE) cell culture	Preclinical	Cells are obtained via ovarian biopsy and placed in culture in the presence of estrogen – this can result in the development of new eggs from the cells.

Source: Edison Investment Research

OvaTure: Harnessing EggPCs to create new eggs

OvaScience's second product, OvaTure, aims to create new, fertilisable eggs using a woman's own EggPC. This could, if successful, allow women with poor-quality eggs (or lack of eggs) to undergo IVF using their own mature, high-quality eggs. As discussed earlier, there are many reasons for poor-quality eggs including increasing age, diabetes, cancer and chemotherapy. In fact, some chemotherapy drugs (ie cyclophosphamide) can permanently stop the ovaries from producing eggs. Successful development of OvaTure could potentially transform the IVF procedure by:

- Allowing women to undergo IVF with their own high-quality (nondonor) eggs, allowing couples to preserve a genetic match and reducing (or eliminating) the need for donor eggs; and
- Reducing (or eliminating) the need for hormonal hyperstimulation and surgical egg retrieval, as mature eggs would be generated in vitro from the woman's own EggPC.

Strong scientific rationale for OvaTure

The basic science underpinning OvaTure has been discussed earlier. In summary, research by Dr Tilly and others has shown that mouse EggPC can produce new eggs in vitro that can be matured, fertilised and produce healthy offspring. In addition, mouse EggPC can be coaxed into making new eggs by stimulation with small molecule drugs (the HDAC inhibitor trichostatin) and unidentified blood factors. Dr Tilly subsequently showed that human EggPC could be matured into eggs, which exhibit a genetic signature suggesting that they could be fertilised.

The obvious next step is to determine whether eggs derived from human EggPC can be fertilised and form normal, early-stage embryos. A broad outline of the preclinical development plan is as follows:

- Optimise the culture conditions used *in vitro* to transform EggPC into mature, fertilisable eggs – includes testing various proteins and growth factors alone, and in combination, to identify the optimal composition and sequence of proteins/factors necessary for creating new eggs.
- Further preclinical mouse studies to confirm earlier research – fertilisation and pregnancy rates, healthy live births, congenital malformations and reproductive ability of the offspring.
- Preclinical study using human EggPC – attempt to mature human EggPC *ex vivo* into fertilisable eggs using the optimised culture conditions.

Positive preclinical data could trigger human trials in 2015

OvaScience believes that the successful completion of preclinical studies (2014) could lead to initiation of a human clinical study in 2015. In contrast to AUGMENT, the company believes that OvaTure would be regulated as a new biological product (BLA). This would need FDA approval to run clinical studies (ie Investigational New Drug, or IND, submission), an extensive clinical development programme, and thorough premarket review and BLA approval.

OvaTure represents upside to our forecasts

Given its early stage and the lack of human EggPC proof-of-concept, we currently exclude OvaTure from our financial model. As such, OvaTure represents upside to our current forecasts and valuation for OvaScience. FDA approval for human clinical trials could be the catalyst for including OvaTure within our model.

Valuation

We value OvaScience at $146m, or $10.20 per share, based on a risk-adjusted NPV analysis. The breakdown of our valuation model is illustrated in Exhibit 13. We forecast 10-year cash flows from AUGMENT in the US market only and discount using a 12.5% WACC and 1% terminal growth rate. With cash equating to $1.0 per share, our unrisked adjusted valuation is $17.00; applying a 60% probability of launch to AUGMENT to reflect clinical and regulatory risks, lowers our valuation to $10.20 per share. This represents 20% upside to OvaScience's current market cap (based on 14.3m common stock outstanding) of $121m and $8.50 share price.

Exhibit 13: rNPV valuation model and key assumptions

Product	Indication	rNPV ($m)	rNPV/ share ($)	Prob. of success	Launch	Peak sales ($m)	Key assumptions
AUGMENT	IVF	145.2	10.2	60%	2014	160	US market only: women >35yrs failing at least 2 IVF cycles; peak 25% share of 25k eligible women; price $15,000
R&D expenses		(3.1)	(0.2)				Preclinical R&D expenses for OvaTure
G&A expenses		(8.9)	(0.6)				General overhead costs not attributable to AUGMENT
Capex		(1.4)	(0.1)				Laboratory supplies and equipment
Net cash		14.3	1.3				Forecast net cash at YE-2013
Total		**146.1**	**10.2**				

Source: Edison Investment Research

While the investment case is subject to higher than normal risks, we view a 60% risk adjustment on AUGMENT as adequately reflecting the near-term clinical and regulatory risks associated with the product. As such, there is significant upside potential linked to positive AUGMENT data and US commercial launch; unwinding our risk adjustment would increase our rNPV (+66%) to $17.0. Moreover, we do not yet attribute any value to AUGMENT in ex-US markets or preclinical programmes (OvaTure), so these represent pure upside.

Our $160m peak sales estimate for AUGMENT assumes a US launch in H214, pricing of $15,000 per procedure (in addition to standard IVF costs), and 25% penetration of the initial target market of 25,000 women (age over 35, failed two prior IVF cycles). These assumptions underpin our base-case valuation of $10.20. We have conducted scenario analyses to assess the impact of different price, market share, and probability of success assumptions on our NPV valuation (Exhibits 14 and 15).

Exhibit 14: rNPV with different AUGMENT price and market penetration assumptions

		AUGMENT price ($)		
		10,000	15,000	20,000
Market penetration (%)	20	4.9	7.9	10.9
	25	6.4	10.2	13.9
	30	7.9	12.4	16.9

Source: Edison Investment Research

Exhibit 15: rNPV with different AUGMENT risk adjustment and market penetration assumptions

		AUGMENT prob. of success (%)		
		40	60	80
Market penetration (%)	20	5.3	7.9	10.6
	25	6.8	10.2	13.6
	30	8.3	12.4	16.6

Source: Edison Investment Research

In the unlikely scenario that AUGMENT use is restricted solely to women aged 38-42 with multiple IVF cycle failures (ie AUGMENT study population) our NPV valuation falls to $8.10 per share. We believe, however, that the more likely scenario is AUGMENT expansion into earlier lines of use (women failing just one IVF cycle), supported by further clinical data (extension study) or positive post-launch

experience. Exhibit 16 outlines the impact on our valuation from expanding the AUGMENT-eligible population from 19,500 (age 38-42, failed 2 IVF cycles) to 35,000 (age >35, failed 1 IVF cycle).

Exhibit 16: NPV valuation with different target population and penetration assumptions

		US target population		
		19,500	25,000	35,000
Market penetration (%)	20%	6.2	7.9	10.9
	25%	8.1	10.2	14.0
	30%	9.9	12.5	17.0

Source: Edison Investment Research

Sensitivities

OvaScience is exposed to the usual biotech company development risks, the unpredictable outcomes of clinical trials, decisions by regulators, the success of competitors, financing and commercial risks. Specifically, there is particularly high sensitivity to the outcome of the AUGMENT study, where negative efficacy and/or safety data could represent a significant setback. Conversely, positive AUGMENT data (H214) could achieve a significant re-rating in the company's valuation. Investors should be aware that AUGMENT has never been tested in humans, and that related approaches (cytoplasmic and mitochondria transfer) have only been tested in small clinical trials. While results of these human proof-of-concept studies are generally supportive, the limited dataset makes it difficult to predict the likely success of AUGMENT. Regulatory risk associated with the 361 HCT/P pathway is another key sensitivity. Although AUGMENT appears to qualify as a 361 HCT/P, the FDA could decide to regulate AUGMENT as a new drug/biologic requiring premarket approval – this could entail a large pivotal study that significantly increases development costs and timelines, and require an additional capital raise.

Financials

OvaScience ended Q312 with cash of $35.1m. R&D and G&A expenditure for the first nine months were $3.9m and $5.4m respectively, leading to operating cash outflow of $9.3m (c $3m/quarter). We expect operating expenses to increase significantly in 2013 and 2014, which primarily relates to costs associated with the AUGMENT study and initial commercialisation activities. Our model, in line with company guidance, projects that OvaScience has sufficient cash to complete the AUGMENT study and fund the potential US commercial launch in H214. Of note, our model does not assume any revenue (upfront/milestones) from potential future licensing deals on AUGMENT (ex-US) or OvaTure.

OvaScience has 14.3m shares outstanding and additional stock options totalling 2.1m. In early November, 7.6m shares were registered for sale on the OTCBB; the remaining 6.6m shares will become eligible for sale over 2013-15 once various lock-up agreements expire. Since inception in April 2011, OvaScience has raised $48.3m ($45.3m net) in three private rounds: sale of 6.2m share of Series A convertible preferred stock for $6.2m (July 2011); sales of 6.8m Series B stock for $37.2m (March 2012); and a private placement of 0.9m common shares for $4.9m (August 2012). The private placement triggered the conversion of Series A and B stock into shares of common stock: each share of Series A converted on a 1-for-2 basis (ie 3.1m shares) while each Series B converted at 1-for-1.

OvaScience's major shareholders are the Founders (21.4%), Longwood Fund (20.1%), Bessemer Venture Partners (14.6%), Fidelity (8.0%), General Catalyst Partners (7.6%) and BBT Funds (5.7%).

Exhibit 17: Financial summary

	2011	2012e	2013e
Year ending 31 Dec			
PROFIT & LOSS ($'000)			
Revenue	0	0	0
EBITDA	(2,278)	(12,949)	(15,946)
Operating profit (before GW and except)	(2,278)	(12,999)	(16,046)
Intangible amortisation	0	0	0
Exceptionals/special Items	0	0	0
Share-based payment	(447)	(979)	(1,000)
Operating profit	(2,725)	(13,978)	(17,046)
Net interest	0	175	224
Profit before tax (norm)	(2,278)	(12,824)	(15,822)
Tax	0	0	0
Profit after tax (norm.)	(2,278)	(12,824)	(15,822)
Average number of shares outstanding (m)	0.9	7.9	14.3
EPS - normalised (c)	(250.6)	(162.2)	(110.9)
Dividend per share (c)	0.0	0.0	0.0
EBITDA margin (%)	N/A	N/A	N/A
Operating margin (before GW and except) (%)	N/A	N/A	N/A
BALANCE SHEET			
Fixed assets	0	979	1,379
Intangible assets	0	0	0
Tangible assets	0	979	1,379
Investment in associates/other non core assets	0	0	0
Trade investment & others	0	0	0
Associated with assets held for sale	0	0	0
Current assets	4,585	30,683	14,252
Stocks	0	0	0
Debtors	0	0	0
Cash	4,541	30,474	14,252
Other	44	209	0
Current liabilities	(675)	(1,810)	(1,810)
Creditors	(675)	(1,810)	(1,810)
Other creditors	0	0	0
Short-term borrowings	0	0	0
Provisions and other current liabilities	0	0	0
Associated with assets held for sale	0	0	0
Long-term liabilities	(6,287)	0	0
Long-term borrowings	0	0	0
Deferred taxation	0	0	0
Other long-term liabilities	(6,287)	0	0
Net assets	(2,377)	29,852	13,821
CASH FLOW			
Operating cash flow	(1,560)	(11,814)	(15,946)
Net interest	0	175	224
Tax	0	0	0
Capex	0	(704)	(500)
Purchase of intangibles	0	0	0
Acquisitions/disposals	0	0	0
Financing	6,101	38,276	0
Dividends	0	0	0
Other	0	0	0
Net cash flow	4,541	25,933	(16,222)
Opening net debt/(cash)	0	(4,541)	(30,474)
HP finance leases initiated	0	0	0
Other	0	0	0
Closing net debt/(cash)	(4,541)	(30,474)	(14,252)

Source: Edison Investment Research

Edison investment research

Contact details	Revenue by geography
215 First Street, Suite 240, Cambridge, MA 02142 USA +1 617 902 0682 www.ovascience.com	N/A

CAGR metrics		Profitability metrics		Balance sheet metrics		Sensitivities evaluation	
EPS 2010-14e	N/A	ROCE 2013e	N/A	Gearing 13e	N/A	Litigation/regulatory	●
EPS 2012-14e	N/A	Avg ROCE 2010-14e	N/A	Interest cover 13e	N/A	Pensions	○
EBITDA 2010-14e	N/A	ROE 13e	N/A	CA/CL 13e	N/A	Currency	○
EBITDA 2012-14e	N/A	Gross margin 13e	N/A	Stock turn 13e	N/A	Stock overhang	●
Sales 2010-14e	N/A	Operating margin 13e	N/A	Debtor days 13e	N/A	Interest rates	○
Sales 2012-14e	N/A	Gr mgn / Op mgn 13e	N/A	Creditor days 13e	N/A	Oil/commodity prices	○

Management team

CEO and Co-founder: Dr Michelle Dipp, MD, PhD

Co-founder of OvaScience in 2011 and serves on the board of directors. Partner and founder of Longwood Fund. Co-founder of Alnara (acquired by Eli Lilly) and Verastem. Previously SVP and Head of CEEDD at GlaxoSmithKline (GSK). Prior to this, head of BD at Sitris (acquired by GSK). Worked in healthcare private equity at The Wellcome Trust, London. MD and PhD from the University of Oxford.

Chief Commercial Officer: Christopher Bleck

Appointed CCO early 2012, was COO during 2011. Previously President and CEO of Incept Biosystems, CEO Intact Medical Corporation, VP of commercial operations at Cytyc Corporation. Prior to this, 18 years in senior management at Abbott Laboratories including position as president & general manager, Abbott Canada. BS degree in Pharmacy and MBA from University of Connecticut.

CSO and co-chair SAB: Scott Chappel, PhD

Chief Scientific Officer since 2011. Previously chief scientist at Serono directing research that led to development of six FDA-approved and marketed products. Most recently, CSO and COO of Tokai Pharmaceuticals. Prior to this, executive at various biotech companies including Dyax, Diacrin and Integrated Genetics. PhD from University of Maryland School of Medicine.

Chief Operating Officer: Alison Lawton

Appointed COO early 2012. Previously SVP and General Manager of Sanofi Biosurgery (formerly Genzyme Biosurgery). Prior to this, SVP of Global Market Access for Genzyme. Served two terms as Industry Representative on the FDA's Cell & Gene therapy Advisory Panel. Currently Board member of Cubist Pharma and Verastem. Holds BSc Hons in Pharmacology from King's College London.

Principal shareholders	(%)
Directors and executive officers	21.4
Longwood Fund	20.1
Bessemer Venture Partners	14.6
Fidelity Investments	8.0

Companies named in this report

Agenus Inc (AGEN), Auxigyn, Merck KGaA (MRK) Novocellus, ORIGIO a/s (part of The Cooper Companies, COO), Ovacyte

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