

28 February 2011

Merrion Pharmaceuticals

Year end	Revenue (€m)	PBT* (€m)	EPS* (c)	DPS (c)	P/E (x)	Yield (%)
12/08	1.3	(5.1)	(0.3)	0.0	N/A	N/A
12/09	6.3	(1.6)	(0.1)	0.0	N/A	N/A
12/10e	4.6	(2.0)	(0.1)	0.0	N/A	N/A
12/11e	2.5	(3.7)	(0.2)	0.0	N/A	N/A

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

Investment summary: Project diversification

Merrion has signed three evaluation contracts, including Novo and a top 10 pharma to use its delivery technology for up to six products. This should give a set of new development projects by H211. On Orazol, academic studies show efficacy in post menopausal women with early-stage breast cancer. This will be the new Orazol target indication for Phase III and can be developed once a partner is signed. Novo is developing oral insulin and GLP-1 but has licensed a second delivery system.

Partnering deals in Q4 2010

Merrion signed three technology evaluation deals in Q4, with Rebel, an unnamed top-10 pharma company and on a third Novo project. Of these, several could become full-scale, fully funded development projects from Q311 with eventual royalties. These deals show the broad applicability of Merrion's oral delivery technology.

Orazol in post-menopausal breast cancer

The December 2010 AZURE data caused a re-evaluation of the development track for Orazol. It will now be developed for early-stage, post-menopausal breast cancer. The Phase III study duration of at least three years depends on selecting stage 2/3 high-risk patients. We anticipate an Orazol deal in 2011. A direct skeletal events comparison to Zometa would be onerous via the FDA, but a skeletal biomarker study is planned for EMA review that could also allow US registration.

Novo hedges its delivery strategies

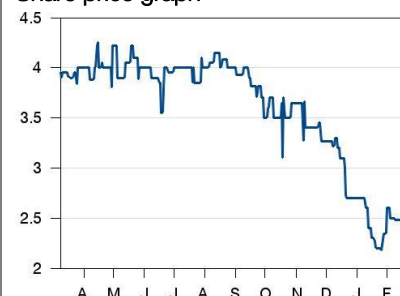
The Novo development project on oral insulin is progressing and we expect data in H211. The first clinical GLP project has ended and development has switched to a second generation analogue. Novo has also started a third, non-diabetes evaluation project. However, Novo has hedged its delivery bets by licensing Emisphere's oral delivery technology for insulin. Different systems may yield different insulin profiles.

Valuation: Potential for rapid value growth on partnering

We continue to indicate a value of €103m or €5.81/share using a DCF model. Orazol partnering would remove a key uncertainty and we see this as likely following the AZURE data and FDA agreement. Cash will rise as deals are signed: a further \$1m plus milestones are due following Novo insulin trials.

Price €2.48
Market cap €42m

Share price graph



Share details

Code 3MP
Listing IEX
Sector Pharmaceuticals
Shares in issue 17.1m

Price

52-week High Low
€4.20 €2.19

Balance sheet as at 31 December 2009

Debt/equity (%) N/A
NAV per share (c) 35
Cash (€m) 7.2

Business

Merrion is an Irish company with oral delivery technology (GIPET) to reformulate injectable drugs into oral formulations. Its lead projects are Orazol, insulin and GLP-1 (in collaboration with Novo Nordisk). It carries out contract projects.

Valuation

	2009	2010e	2011e
P/E relative	N/A	N/A	N/A
P/CF	N/A	N/A	N/A
EV/Sales	N/A	N/A	N/A
ROE	N/A	N/A	N/A

Geography based on revenues

	UK	Europe	US	Other
0%	100%	0%	0%	0%

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Investment summary: Project diversification

Merrion was created in 2004 through the acquisition of some of Elan's drug delivery technology and listed on the Irish Enterprise Securities Market (ESM) in December 2007 at €4.05 a share (raising €8m gross at a capitalisation of €67.2m). Merrion uses its GIPET technology to reformulate injectable pharmaceuticals, many already marketed, for oral delivery and to improve delivery profiles. After agreement with the FDA, Orazol (an oral form of Zometa, Novartis) will be positioned as an adjuvant treatment for early-stage breast cancer in post-menopausal women requiring a single Phase III study. Academic trial data shows strong support for this indication. Statistical complexities with Zometa's original registration mean that a direct equivalence study in the US would have been onerous. A non-inferiority biomarker-based study for bone metastasis will be run in Europe and could lead to a US label alongside the breast cancer study. There are two \$58m funded collaborations with Novo (to develop oral insulin and GLP-1). The first trials, in oral insulin, will report in H211; an exploratory clinical GLP-1 study was terminated but the project continues with better analogues. Three new evaluation deals announced in late 2010 cover six products. A licensing deal for Orazol is possible in 2011; Phase III trials could enable marketing from 2015.

Valuation: DCF value of €5.50 per share pre Orazol partnering

We continue to indicate a value of €103m or €5.81/share using a DCF model. Orazol partnering would remove a key uncertainty and we see this as likely following the AZURE data and FDA agreement. Cash will rise as deals are signed; a further \$1m plus milestone is due following Novo insulin trials. However, valuation has a high degree of uncertainty until a deal is signed and some of the established portfolio projects have seen little development for some time.

Sensitivities

A major sensitivity lies in the timing and terms of the Orazol deal. The cash and logistic requirements of an early-stage breast cancer trial probably mean a partner is needed to run the Phase III study efficiently. The timing of the trial outcome relies on a high enough event rate (cancer progression within two years of entry) and gaining enough high-risk patients in the database. If event rates are below expectations, any trial will become prolonged. Management notes that detailed modelling and a science advisory board comprising lead investigators from key academic trials have been used to mitigate this risk. Non-injected insulin has been difficult to develop but the Novo collaboration seems to be running very well although Novo is working with two technologies, the other being from Emisphere. Clinical trials are now underway. The GLP-1 market is highly competitive, although an oral biological product would hold a unique position. Novo is now developing a second generation oral GLP-1 but this is many years from possible market entry. The new set of evaluation deals might develop into a broader, funded portfolio of projects. This is needed to broaden out the portfolio and provide cash.

Financials

Interim FY10 revenues to 30 June 2010 were €2.75m with a gross margin of 73%. In the second half, revenues will have fallen off as much of the manufacturing and preclinical work on the Novo contract has been completed. Clinical trials are run and paid by Novo directly. Operating costs in H1 were €2.8m. Cash was €5.9m on 30 June. Given that further, fully funded, evaluation deals were signed in late 2010, we expect revenues to hold up although the reported revenues depend on accounting recognition of cashflows. An insulin milestone is expected from Novo in H111.

Outlook: Utilising GIPET delivery

Merrion's portfolio is based on gastrointestinal permeation enhancement technology (GIPET) acquired from Elan. GIPET uses well-known compounds to enhance drug absorption, and all ingredients are designated by the FDA to be Generally Regarded As Safe (GRAS, a food safety category), which simplifies regulatory submission. These are formulated using an enteric coated tablet to release the drug in the duodenum (upper small intestine). GIPET offers a broad platform to deliver many different peptides and hard-to formulate small molecules. It is allowing Merrion to develop potential new products. Three further deals and collaborative deals were signed in late 2010. These deals extend its portfolio and revenue base. The major current collaboration is with Novo Nordisk. The current pipeline is in Exhibit 1.

Exhibit 1: Merrion's R&D portfolio

Product	Drug uses	Notes	Merrion clinical status
Orazol (zoledronic acid) /MER-101	Adjuvant therapy given with endocrine therapy to postmenopausal women with Stage 2/3 breast cancer..	Zometa (Novartis) is dosed as a 4mg iv infusion every month for Novartis's patents expire in 2013. The Phase III needed to show efficacy in disease-free survival will take at least three years.	Phase II biomarker data indicate that weekly oral Orazol (20mg) is as effective as monthly iv Zometa (4mg). A large partner would conduct registration trials,
Almerol/ MER-103	Alendronate for osteoporosis.	Fosamax (Merck) generic since 2008; other bisphosphonate patents expire 2011-2.	Phase I showed that 6mg Almerol is equivalent to 70mg Fosamax.
Oral insulin analogue	Diabetes. Either with meals as a supplement or as a long-acting version.	Potential major innovation with more 'natural' mode of insulin action but must deliver as a predictable dose and time.	Clinical evaluation of candidates. Will require an extensive clinical development programme.
Oral GLP-1 analogue	Type 2 diabetes.	Byetta (exenatide, Lilly) is twice daily sc. Victoza (liraglutide, Novo), a daily sc formulation has FDA and EMEA approval.	Preclinical evaluation of candidates. Will require an extensive clinical development programme.
MER-104 (acyline)	GnRH agonist for prostate/breast cancer.	Would require full clinical development. Addresses a large market but with many established products.	NIH has run trials in 125 volunteers. Merrion has run a Phase I and a four patient dose escalation study.
MER-102/ fondaparinux	Factor Xa antagonist thrombosis and embolism following surgery.	Arixtra (GlaxoSmithKline) is available as daily 2.5mg sc injection. It is typically administered for five to nine days.	Preclinical evaluation showing 13-17% bioavailability. Partnering interest.
Evaluation stage projects			
Novo Nordisk	unknown	Evaluation of undisclosed compound.	Preclinical, no additional information
Top 10 Pharma	Unknown	Evaluation of three compounds	Preclinical, no additional information
Rebel	Unknown	Evaluation of two compounds.	Preclinical, no additional information
Ferring	unknown	Evaluation of undisclosed compound.	Preclinical, no additional information

Source: Merrion Pharmaceuticals reports, Edison Investment Research commentary

Deals – building a base of externally funded projects

In a spurt of activity in late 2010, Merrion signed three technology evaluation deals. The move to the new facility over 2010 has given the capacity to run these extra projects.

Novo and Merrion will evaluate a new, undisclosed compound using the GIPET delivery system. This may progress to a full scale project in H211. Upon signing a licence agreement, Novo can exercise an option and buy €1.5m of equity at €2.73 per share. Merrion can request Novo to acquire a further €0.5m. We anticipate that these might be exercised later this year.

A top 10 pharma company has retained Merrion to test three compounds with delivery issues. If the tests are successful, one or more might license GIPET for clinical stage development with potentially additional contract research.

Rebel Pharmaceuticals has retained Merrion, in effect, to act as its drug development operation. Rebel appears to be a private, virtual US pharmaceutical company associated with the CEO of Edgemont Capital, a US financial services consultancy supplying strategic services to like science companies. We understand that both of these product concepts are relatively simple to adapt to

GIPET use and so is likely to lead to a product development licence by mid 2011. If so, deal terms have already been agreed. We have no financial data on Rebel.

Ferring – a longstanding evaluation contract continues to progress.

Orazol: The early-stage breast cancer opportunity

There is extensive clinical evidence¹ showing that zoledronic acid affects cancer cells directly and that use of zoledronic acid is cost effective.² Only nitrogen containing bisphosphonates have this cancer cell attack function, others, normally used in treatment of osteoporosis like Fosamax (alderonate), do not. A therapeutic activity attacking cancer cells would run alongside the proven bone protective attributes of bisphosphonates to stop metastatic bone invasion.

Two trials are crucially important in this hypothesis, ASCBG-12 and AZURE, with various other studies, such as ZOFAS and ZOLOFT, adding information. In November 2010, the FDA agreed with Merion a route to approval based on early-stage breast cancer.

ABCSG-12

In 2009, data from [ABCSG-12](#), a 1,803 pre-menopausal patient study, showed that zoledronic acid (ZA) given 4mg every six months increased disease free survival to 94% vs 90.8% of patients on endocrine therapy alone at the median follow up of 47.5 months, Exhibit 2. This 3.2% gain was an impressive result. The risk of disease progression fell by 36% to an odds ratio of 0.64. On the back of this data, Novartis filed a speculative application with the FDA in late 2009 to extend the label of Zometa into early stage breast cancer. This was a difficult submission as it was based on an academic, not a regulatory, study. It seems to have been withdrawn during 2010.

Exhibit 2: Video discussion of ABCSG-12 trial results



Watch [video link](http://www.ecancermedicalscience.com/tv/?play=521) (<http://www.ecancermedicalscience.com/tv/?play=521>)

Source: ecancer, data at: [N Engl J Med. 2009 Feb 12;360\(7\):679-91.](#)

In view of later data, the important aspect of the ABCSG-12 study was its choice of endocrine therapy. This was either anastrozole (Arimidex, AstraZeneca) plus goserelin (Zoladex, AstraZeneca) or tamoxifen plus goserelin. Anastrozole is an aromatase inhibitor that blocks the synthesis of the hormone oestrogen. Goserelin is a peptide hormone given as an implant. It blocks the hormone signal to the ovaries so they cease oestrogen production. Tamoxifen blocks the action of oestrogen on cells, particularly hormone sensitive breast cancer cells. ABCSG-12 found no survival differences between the two hormone therapies if zoledronic acid was not given. It therefore appeared that early-stage breast cancer could be treated with zoledronic acid. However, all arms of the study received goserelin and so all the tumours were in a low oestrogen environment.

AZURE

AZURE recruited 3,359 patients to receive adjuvant chemotherapy and/or endocrine therapy, hence all patients received endocrine therapy but did not have to be on goserelin. Each arm was then randomised so half also received zoledronic acid. The study is open label and patients are being followed for 10 years. The zoledronate dose titrated down over a five year period from the metastatic

¹ Lipton A. Should bisphosphonates be utilized in the adjuvant setting for breast cancer? [Breast Cancer Res Treat. 2010 Aug; 122\(3\): 627-36. Epub 2010 May 21.](#)

² Delea TE et al. Cost-effectiveness of zoledronic acid plus endocrine therapy in premenopausal women with hormone-responsive early breast cancer. [Clin Breast Cancer. 2010 Aug 1; 10\(4\): 267-74.](#)

cancer dose of four-weekly administration to an osteoporosis type dose of twice per year. As such, the zoledronic acid regimen is not optimised for efficacy. Alternative dosing schemes may offer better results.

On 9 December 2010, an interim analysis of the [AZURE](#) trial was presented.³ This analysis was run as a lower rate of disease progression events was occurring than expected, requiring the trial to extend till 2012. It was felt that the importance of the trial justified the small loss of statistical power caused by this analysis. The overall results are available as an [abstract](#); the data is shown in Exhibit 3 and the survival curves shown in Exhibit 4.

Exhibit 3: Interim analysis of AZURE

Menopause status	Patients	Arm	Events	Deaths	%	Hazard Ratio	p
Both pre and post	1,678	control	375	276	16.4%	0.98	0.79
	1,681	zoledronate	377	243	14.5%		
Pre and peri	1,127	control	228	156	20.2%	1.01	0.93
	1,131	zoledronate	261	157	23.1%		
Post	551	control	147	120	26.7%	0.71	0.017
	550	zoledronate	116	86	21.1%		
Oestrogen Status	Patients	Menopausal	Events	Deaths	%	Odds Ratio	p
High	2,318	Pre and peri	505	NA	22%	1.13	0.02
Low	1,041	Post	247	NA	24%	0.76	

Source: San Antonio Breast Cancer Symposium December 2010

The primary endpoint of the trial is disease-free survival. On the primary endpoint zoledronic acid had no effect with a 0.98 hazard ratio. Secondary endpoints do allow segmentation by menopausal status and this shows a different picture. The overall survival seen in pre-menopausal women was the same whether or not zoledronic acid was given, hazard ratio 1.01.

However, in post-menopausal women, survival among those receiving zoledronic acid was much better. There was a 29% reduced risk of death and the result is significant ($p=0.017$) even though fewer post-menopausal patients are included in this study.

When the odds ratios⁴ are calculated for the impact of zoledronic acid on the separate pre and post menopausal groups, it is clear that if oestrogen is absent, the odds ratio of disease progression shifts from 1.13 in high oestrogen patients to 0.76 in low oestrogen, post-menopausal patients. The two groups are clearly separated using a chi-squared test, $p=0.02$.

The effect of oestrogen was assessed by looking at the disease-free survival rate of the 1,219, high-oestrogen, pre menopausal group in AZURE with all 1,803 ABCSG-12 hormone suppressed patients. This is slightly biased since half of the ABCSG-12 patients had received zoledronic acid as well. A chi-squared test showed that the two populations were different, $p=0.02$.

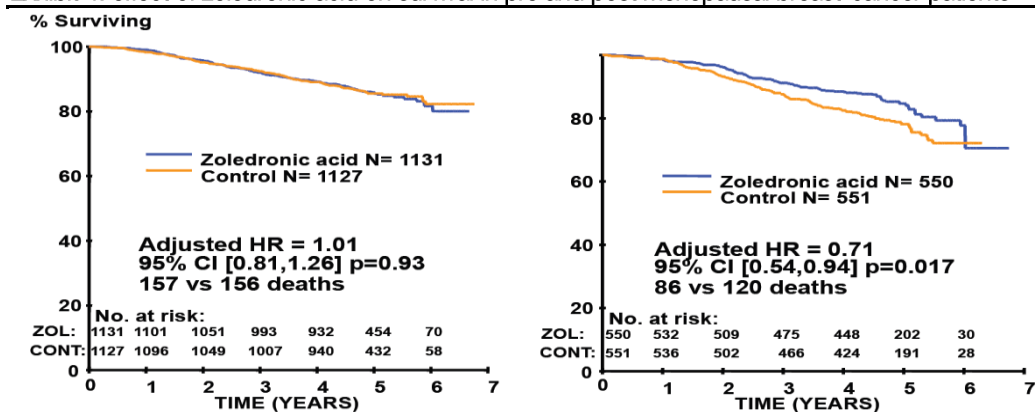
The implication of AZURE taken with ABCSG-12 is that zoledronic acid does not have any survival or disease free progression benefit if oestrogen is present. All women in AZURE received standard endocrine therapy anyway but even small amounts of oestrogen apparently override any zoledronic

³ San Antonio Breast Cancer Symposium Source reference: Coleman RE, *et al.* Adjuvant treatment with zoledronic acid in stage II/III breast cancer. The AZURE Trial (BIG 01/04). SABCS 2010; General Session 4, Friday 10 December 2010 16.15, [S4-5](#).

⁴ Odds and hazard ratios are very similar calculations but there are differences. Hazard ratio is a moving target. A patient who survives one period, say a month, has the hazard ratio of an event (death or progression) in the next period relative to the control arm. So a hazard ratio of 0.71 means there is a 29% reduction in the chance of the event compared to control. Hazard ratios are applied to Kaplan-Meier plots as in Exhibit 4. Kaplan Meir plots the time each patient survived to at that point in the trial. A hazard ratio over 1 means there is an increased chance. An odds ratio is calculated at a particular time point for the treated cohort relative to control cohort and is an absolute value.

acid effect. The effect can only be seen in post-menopausal women on single-agent endocrine therapy or pre-menopausal women on goserelin with additional endocrine therapy.

Exhibit 4: effect of zoledronic acid on survival in pre and post menopausal breast-cancer patients



Source: San Antonio Breast Cancer Symposium December 2010

Other studies

The [Z-FAST](#)⁵ and [ZO-FAST](#)⁶ studies in post-menopausal women are designed to evaluate whether zoledronic acid plus hormone therapy (the aromatase inhibitor, letrozole [Femara]) improved bone density in cancer patients. The reason is that post-menopausal women on endocrine therapy are at particular risk of bone loss and so prone to fracture. These studies randomised patients into two arms, giving one zoledronic acid immediately and the other zoledronic acid starting a year later. They are therefore designed to test if immediate zoledronic acid therapy is beneficial compared to a delay. There is no separate untreated control group.

Both have now reported 36 month data. Z-FAST has a survival secondary endpoint but ZO-FAST does not. It is therefore ironic that ZO-FAST has shown evidence of a survival advantage whereas Z-FAST showed a survival trend (p=0.127) with an absolute decrease of 2.3% in disease recurrence, a bigger study would be needed.

ZO-FAST showed that adding zoledronic acid reduced the risk of disease progression by 41% after three years (p=0.0314). This is consistent with the AZURE subgroup analysis. Bone mineral density also rose in groups immediately treated with zoledronic acid and comparable with ABCSG-12 as those patients had high-levels of hormone suppression.

[Markers](#)⁷ (VEGF and bone peptide fragments) show that regular weekly low-dose zoledronic acid reduced levels of VEGF (the angiogenic hormone) and cut levels of bone markers. There was no survival data from this small, 60 patient study but the marker data implies that tumour growth was more effectively retarded. [Rack](#)⁸ found that zoledronate helped to destroy isolated tumour cells located in the bone marrow in a small prospective 172 patient trial. If these cells persisted, the clinical prognosis was much worse; the findings are statistically significant.

⁵ Brufsky AM *et al.* Zoledronic acid effectively prevents aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: Z-FAST study 36-month follow-up results. [Clin Breast Cancer. 2009; 9: 77-85.](#)

⁶ Eidtmann H *et al.* Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST Study. <http://www.ncbi.nlm.nih.gov/pubmed/20444845>. See also [review](#).

⁷ Zhao X, *et al.* Breast Biomarker alterations with metronomic use of low-dose zoledronic acid for breast cancer patients with bone metastases and potential clinical significance. *Cancer Res Treat.* 2010;124:733-43.

⁸ Rack B *et al.* Effect of zoledronate on persisting isolated tumour cells in patients with early breast cancer. [Anticancer Res. 2010; 30: 1,807-13.](#)

Mechanism of action – a debatable matter

The main theory is that zoledronic acid interferes with the production of isoprenoids (small molecules used to assemble long chains of fatty acids) by inhibiting farnesyl pyrophosphate synthase an enzyme in the mevalonate pathway. Some key signalling GTPase proteins need to be anchored to cell membranes by post-translational farnesylation and geranylgeranylation so zoledronate may interfere with cell signalling. [Knight](#)⁹ has found synergistic action between statins and zoledronate in cell lines which supports this idea. [Karabulut](#)¹⁰ found synergy between retinoic acid and zoledronate to promote apoptosis.

An alternative view from [Todaro](#)¹¹ is that zoledronate causes accumulation of phosphoantigens on the cell surface triggering an immune response. This was done with supposed cancer stem cells. [Cabillic](#)¹² also found that zoledronic acid stimulated an immune response due to stimulation of autologous dendritic cells by isopentenyl pyrophosphate. Zoledronate may cause an increase in this due to its action in blocking enzymes in lipid synthesis.

Any mechanism must take into account the fact that zoledronic acid is very rapidly excreted from the body if it is not incorporated into bone. As it is given infrequently and is fleetingly present in plasma, it must have either a very local long-term effect, as in the bone marrow, or stimulate another process with a much longer duration of action. The immune response concept would offer that possibility. Interference with internal cell signalling seems unlikely to us as the duration of exposure is too short and signalling molecules are rapidly turned over within cells. It would need to be an exceptional apoptosis promoter to have a significant effect. There is no particular reason why any immune effect would be limited to breast cancer and preclinical experiments on prostate and even liver cancer have shown effects.

Orazol development

After prolonged FDA discussion, in November 2010, Merriem and the FDA agreed to develop Orazol for early-stage breast cancer. The original idea was to show equivalence to zoledronic acid in breast and prostate cancer in relation to skeletal events. However, zoledronic acid was approved on an equivalence basis to pamidronate (an old bisphosphonate, now generic, branded Aredia). Showing equivalence to an agent itself approved on an equivalence basis requires complex statistics and a large study or a requirement to run a full registration programme for an indication about to suffer generic competition. These issues are not apparent with the EMA so a biomarker-based non-inferiority trial can be run in bone metastasis. This data, plus data on skeletal events from a breast cancer study, should enable an eventual US skeletal events label to be gained.

A concern with Phase III development for breast cancer indication is the potential size of the trials required and their duration. However, because it will be a 505(b)(2) submission, as zoledronic acid is an approved molecule, only one Phase III is required. The estimated patient numbers are 800-1,000. The recruitment time will be 18 months with patients followed for 18 months and then a 10 month data analysis phase. The number of events is critical to timing and this could be addressed by selecting Stage 2 breast cancer patients who have higher risk factors. An example would be a T4

⁹ Knight LA, Activity of mevalonate pathway inhibitors against breast and ovarian cancers in the ATP-based tumour chemosensitivity assay. [BMC Cancer. 2009; 9: 38.](#)

¹⁰ Karabulut B, *et al.* Enhancing cytotoxic and apoptotic effect in OVCAR-3 and MDAH-2774 cells with all-trans retinoic acid and zoledronic acid: a paradigm of synergistic molecular targeting treatment for ovarian cancer. [J Exp Clin Cancer Res. 2010; 29:102.](#)

¹¹ Todaro M, *et al.* Efficient killing of human colon cancer stem cells by gammadelta T lymphocytes. [J Immunol. 2009; 182: 7,287-96.](#)

¹² Cabillic F, *et al.* Aminobisphosphonate-pretreated dendritic cells trigger successful Vgamma9Vdelta2 T cell amplification for immunotherapy in advanced cancer patients. [Cancer Immunol Immunother. 2010; 59: 1,611-9.](#)

tumour, that is, one invading the skin or chest wall even if not yet spread beyond the breast and immediate lymph nodes. An independent monitoring committee will track the trial so the results can be analysed once enough events have occurred rather than on a set time period.

The trial will be of sufficient size and complexity to need a major partner and ideally a deal will be signed in 2011; this should be a major share price catalyst. Assuming a deal by mid 2011, the trial might start in H112 implying recruitment by mid 2013 and enough events by H215. Data analysis and documentation could lead to a filing in H116 with approval on fast track in H216 or more likely H117.

Breast cancer trends

The rate of breast cancer diagnosis is 338 women per 100,000 population over 50 as against 43 per 100,000 under 50. The US and Europe have fairly flat demographic structures with increasing numbers over 50s. In the US, there are about 50m women over 50. This would indicate at least 160,000 new breast cancer diagnoses per year in post-menopausal women. Of these, maybe 30% will be stage 2/3 indicating a possible market of c 50,000 new cases per year. As life expectancy is good, over five years, this could develop into a potential treated US patient population of 250,000. At \$5,000 per year, this equates to about \$1.2bn of sales. This could be increased by 50% for the EU (with tougher national pricing) with further potential in emerging markets. Japan will also be a major market but can take longer to develop for regulatory reasons.

Denosumab update

Xgeva (denosumab, Amgen) is also now indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumours but not for the prevention of skeletal-related events in patients with multiple myeloma. So far, sales of [Xgeva](#) (and [Prolia](#), the osteoporosis version of denosumab) have been low but the launch processes are still underway. Prolia sold \$30m in 2010, \$20m in Q4. Xgeva sold an impressive \$8m given its approval only on 18 November. On balance, Xgeva might have a much better market.

As zoledronic acid prevents skeletal events and seems to affect cancer cells, it would appear to have an advantage, at least in post-menopausal women. Both therapies are given every four weeks, Xgeva by injection and zoledronic acid by infusion.

Partnership with Novo

The new evaluation with Novo, with pre-arranged terms, shows the strength of this relationship. There are two running projects: oral insulin and oral GLP-1 both in phase I/II clinical development. This section updates our note of 14 September 2009.

Oral insulin

In 2009, Novo claims to have had a 51% share of the total insulin market making this worth €8.1bn (\$10.9bn); Novo's sales were c €4.3bn. Of this, the 2009 global modern insulin market was worth around €6.2bn (c \$8bn). Companies have tried to develop products that avoid injection but this has failed commercially even when solutions have been developed.¹³ Current oral insulin development has been small-company based¹⁴ but without novel insulin analogues.

¹³ Inhaled insulin (Exubera, Pfizer) failed commercially and was withdrawn in 2008. Mannkind (US listed) has an ultra-rapid mealtime inhaled insulin (Afresa). The FDA issued a compete Response letter in January 2011 requiring two further clinical trials that will take at least 18 months assuming they can be funded. Genex (Canada) has an oral spray, Oral-lyn, approved in Ecuador and Lebanon and recruitment into a US Phase III study is ongoing in type 1 diabetes (data perhaps by 2011).

¹⁴ Most small company development projects in this space have stalled or ceased since our last full review. [Oramed Pharmaceuticals](#) (a US-listed Israeli company) has reported positive Phase IIa data on its oral insulin (ORMD-0801) in type 1 diabetics.

The current oral insulin programme with Merion appears to be a top-up insulin to give a boost just before a meal. In that it is similar to short acting insulin like Humalog (lispro), the market leader, which is injected about 15 minutes before a meal. Humalog sales in 2009 were \$1.96bn. A diabetes clinical programme could take at least six years to run, indicating sales from 2017.

An interesting comment was made on 7 September 2010, by the Novo CSO, to the effect that oral basal insulin would be in the clinic in by Q211. We assume this will use GIPET delivery. Novo also has a deal on another oral insulin delivery technology using Eligen® technology signed 22 December 2010 with [Emisphere Technologies](#) but we do not know how these projects relate to each other.¹⁵ Novo stated that oral programmes would drive Novo's growth in five to 10 years. To date, oral insulins have suffered from low delivery efficiency.¹⁶

A basal oral insulin might be more suitable, and easier to develop, than a short acting, oral pre-meal insulin. This is because a short-acting insulin needs to deliver known quantities of insulin in a known time to offset the post prandial glucose peak. An oral basal insulin just needs to average over a longer period and is not expected to deal with sudden glucose peaks. This would need appropriate, long-lasting insulin analogues. An oral basal insulin could potentially be used as an early-stage therapy in Type II diabetics. Insulin is used in late stage patients but it is known that giving it earlier can be therapeutically efficacious in delaying disease progression. This would be a huge market if it could be developed but the trials required mean it is at least 10 years away.

It is known that oral insulin can be delivered, and insulin works, so we assume a 20% probability of reaching the market, high for a preclinical product, and a \$1bn+ potential; the royalty will be mid-single digit (we assume 5%). The deal with Novo has \$58m of milestones. We assume that about a third is development related, with the rest paid on approval and on sales targets being reached.

Oral GLP-1

This market was pioneered by Amylin and Lilly with Byetta (exenatide). Byetta is a twice per day injectable biological product, with 2009 sales of \$795m (but \$667m in the US, down 2%); Byetta mimics natural GLP-1.¹⁷ Victoza (liraglutide) is a GLP-1 biological drug from Novo which was EMEA approved in July 2009 and FDA approved in January 2010.¹⁸ It has gained about a quarter of the US market helped by a once daily formulation vs Byetta's twice daily injection; it is reported to be getting a 33% share of new prescriptions. Current Phase III products include GSK/HGS Syncria (albiglutide) and Lilly's GLP-1-Fc (dulaglutide). Both are long-acting, fusion-protein products.

The GLP-1 related small-molecule products, Januvia, Onglyza and Galvus, are also directed to early to mid-stage type 2 patients. Other oral small-molecule products are in development. The market could reach \$3-5bn by 2012. This is competitive, big-pharma sales territory.

¹⁵ The Emisphere agreement is for \$57.5m in potential milestones, of which \$5m is upfront, plus royalties, this looks similar to that with Merion. Emisphere's technology may have been revived by use of Novo's insulin analogues. The few published clinical studies on Emisphere's technology indicated unimpressive performance against Metformin.

¹⁶ Heinemann L and Jacques Y. Oral insulin and buccal insulin: a critical reappraisal. [J Diabetes Sci Technol. 2009; 3: 568-584.](#)

¹⁷ Byetta improves insulin sensitivity and glucose regulation. Sales, mostly US, were \$678m in 2008 with growth of 7%. Sales slowed abruptly from August 2008 after an FDA alert that that the drug could trigger pancreatitis. Sales may be \$632m or less in 2009 based on Q109 data, although the clinical link with pancreatitis is not verified. An NDA has been filed for a once-per week version of Byetta. This uses a microencapsulation technology (Medisorb) from Alkermes.

¹⁸ The FDA committee was ambiguous with regard to a rare cancer risk based on rodent data so there are some recommendations about not using in first line therapy and avoiding patients with certain cancer risks.

The other development was that Amylin's Bydureon (partnered with Lilly), a once per week Byetta formulation, was given a complete response letter by the FDA due to cardiovascular concerns. A QT study will need to be run to show safety delaying any FDA approval till at least mid 2012.

The oral GLP-1 product in preclinical development by Merrion and Novo is probably based on liraglutide and its analogues modified to make them protease resistant and therefore more suited to oral delivery. It is difficult to be clear about the commercial implications and the probability of success as no data on the possible products are available and the market itself is still developing.

Any oral GLP-1 needs to be clinically differentiated from the oral small-molecule alternatives to achieve blockbuster revenues. As a preclinical product, the standard of success is 5%, but we would see this as too low and assume c 10% at this time. We assume that the royalty will be 5%. The deal appears to be as for oral insulin but with a longer timeframe targeting a 2017-18 launch.

Note that there has been another deal since 2009 as [Emisphere Technologies](#) is working with Novo Nordisk on oral GLP-1 delivery using Eligen. In January 2010, Novo started a Phase I trial.

Valuation

We continue to indicate a value of €103m or €5.81/share using a DCF model. Orazol partnering would remove a key uncertainty and we see this as likely following the AZURE data and FDA agreement. Cash will rise as deals are signed: a further \$1m plus milestone are due following Novo insulin trials. However, valuation has a high degree of uncertainty until a deal is signed and some of the established portfolio projects have seen little development for some time.

Sensitivities

A major sensitivity lies in the timing and terms of the Orazol deal. The cash and logistic requirements of an early-stage breast cancer trial probably mean a partner is needed to run the Phase III study efficiently. The timing of the trial outcome relies on a high enough event rate (cancer relapses within two years of entry) and gaining enough high-risk patients in the database. If event rates are below expectations, any trial will become prolonged. Management notes that detailed modelling and a science advisory board comprising lead investigators from key academic trials have been used to mitigate this risk. Non-injected insulin has been difficult to develop but the Novo collaboration seems to be running very well, although Novo is working with two technologies; the other being from Emisphere. Clinical trials are now underway. The GLP-1 market is highly competitive. Novo is now developing a second generation oral GLP-1 but this is many years from possible market entry. The new set of evaluation deals might develop into a broader, funded portfolio of projects. This is needed to broaden out the portfolio and provide cash.

Financials

Interim FY10 revenues to 30 June 2010 were €2.75m with a gross margin of 73%. In the second half, revenues will have reduced since much of the manufacturing and preclinical work on the Novo contract will have been completed. Clinical trials are run and paid by Novo directly. Operating costs in H1 were €2.8m. Cash was €5.9m on 30 June. Given that further, fully funded, evaluation deals were signed in late 2010, we expect revenues to hold up although the reported revenues depend on accounting recognition of cashflows. Further insulin cash milestones are expected from Novo in H111. We expect full year results in March 2011. Financial projections are shown in Exhibit 5.

Exhibit 5: Financials

Note: Milestone payments from Novo in respect to the oral insulin programme are expected in H111 but are not included in the forecast of revenues or cash. Revenues include deferred income from early Novo deals on insulin and GLP-1 delivery systems. Other deals and projects are likely to occur in 2011 and a major licensing deal on Orazol is indicated at some time

Year end 31 December	€000s	2008	2009	2010e	2011e
		IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue		1,340	6,335	4,600	2,470
Cost of Sales		(420)	(1,256)	(1,179)	(360)
Gross Profit		920	5,079	3,421	2,111
EBITDA		(5,056)	(1,320)	(1,451)	(3,130)
Operating Profit (before GW and except.)		(5,425)	(1,807)	(1,938)	(3,617)
Goodwill Amortisation		0	0	0	0
Exceptionals		0	0	0	0
Other		0	0	0	0
Operating Profit		(5,425)	(1,807)	(1,938)	(3,617)
Net Interest		363	178	(20)	(36)
Profit Before Tax (norm)		(5,062)	(1,629)	(1,958)	(3,653)
Profit Before Tax (FRS 3)		(5,062)	(1,629)	(1,958)	(3,653)
Tax		0	0	0	0
Profit After Tax (norm)		(5,062)	(1,629)	(1,958)	(3,653)
Profit After Tax (FRS 3)		(5,062)	(1,629)	(1,958)	(3,653)
Average Number of Shares Outstanding (m)		16.7	17.1	17.1	17.1
EPS - normalised (c)		(0.3)	(0.1)	(0.1)	(0.2)
EPS - FRS 3 (c)		(0.3)	(0.1)	(0.1)	(0.2)
Dividend per share (c)		0.0	0.0	0.0	0.0
Gross Margin (%)		68.7	80.2	74.4	85.4
EBITDA Margin (%)		N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)		N/A	N/A	N/A	N/A
BALANCE SHEET					
Fixed Assets		788	5,573	5,107	4,641
Intangible Assets		0	558	279	0
Tangible Assets		788	5,015	4,828	4,641
Investment in associates		0	0	0	0
Current Assets		8,893	9,689	5,486	1,962
Stocks		0	0	0	0
Debtors		753	2,192	1,750	1,502
Cash		8,140	7,218	3,736	460
Current Liabilities		(4,009)	(3,679)	(2,420)	(2,130)
Creditors		(4,009)	(3,207)	(1,947)	(1,658)
Short term borrowings		0	(472)	(472)	(472)
Long Term Liabilities		0	(5,516)	(4,053)	(2,506)
Long term borrowings		0	(2,786)	(2,646)	(2,506)
Other long term liabilities		0	(2,730)	(1,408)	0
Net Assets		5,671	6,067	4,120	1,968
CASH FLOW					
Operating Cash Flow		(2,907)	(1,072)	(3,022)	(2,800)
Net Interest		299	212	(20)	(36)
Tax		0	0	0	0
Capex		(135)	(4,816)	(300)	(300)
Acquisitions/disposals		0	0	0	0
Financing		11	1,502	0	0
Dividends		0	0	0	0
Net Cash Flow		(2,732)	(4,174)	(3,342)	(3,136)
Opening net debt/(cash)		(10,870)	(8,141)	(3,960)	(619)
HP finance leases initiated		0	0	0	0
Other		3	(6)	0	0
Closing net debt/(cash)		(8,141)	(3,960)	(619)	2,517

Source: Edison Investment Research

Growth	Profitability	Balance sheet strength	Sensitivities evaluation	
N/A	N/A		Litigation/regulatory	●
			Pensions	○
			Currency	◐
			Stock overhang	○
			Interest rates	○
			Oil/commodity prices	○

Growth metrics	%	Profitability metrics	%	Balance sheet metrics	Company details
EPS CAGR 07-11e	N/A	ROCE 10e	N/A	Gearing 10e	N/A
EPS CAGR 09-11e	N/A	Avg ROCE 07-11e	N/A	Interest cover 10e	N/A
EBITDA CAGR 07-11e	N/A	ROE 10e	N/A	CA/CL 10e	2.3
EBITDA CAGR 09-11e	N/A	Gross margin 10e	74.4	Stock turn 10e	N/A
Sales CAGR 07-11e	N/A	Operating margin 10e	N/A	Debtor days 10e	139
Sales CAGR 09-11e	102	Gr mgn / Op mgn 10e	N/A	Creditor days 10e	155
Address: Biotechnology Building, Trinity College, Dublin 2, Ireland					
Tel +353 1 672.9272					
Fax +353 1 672.9270					
www.merrionpharma.com					

Principal shareholders	%	Management team
European Bioscience Fund I Ltd	19.5	Chairman: Patrick O'Sullivan
Growcorp Group Ltd.	15.4	Chairman since February 2009. Former CEO of Leo Pharma in Ireland and a board member of the parent Leo Pharma Group in Denmark (until 2006). Mr O'Sullivan holds an MBA and is a registered pharmacist. He is also a director of Warner Chilcott.
Declan Ryan	14.5	
AIB plc	7.0	
John Lynch (CEO)	2.7	CEO: John Lynch
Michael McKenna	4.7	Founder of the company and CEO since 2008, COO since 2005 and MD from 2004. Before that, he spent 15 years with Abbott in the US and UK in senior positions. Earlier in his career Mr Lynch held financial positions with Bayer Diagnostics and Ernst & Young.
Bank of Kernal Capital	3.4	
Forthcoming announcements/catalysts	Date *	
Final results	March 2010	CFO: Jonathan O'Connell
Interims	September 2010	Appointed CFO in November 2005. He has over 13 years' experience in international finance and operations. Prior to Merrion, Mr O'Connell was the CFO at Spectel which was sold in 2004. From 1992 to 2000 he was CFO of Trinity Biotech. He joined Trinity from Arthur Andersen.
Companies named in this report		
Novartis, Novo Nordisk, Amgen, GSK, Lilly		

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