

Novogen Limited

NRT

Monday, 8 October 2007

Phenoxodiol in Phase III Clinical Trials

Recommendation Speculative Buy - When the Price Stabilises

The core focus is on anti-cancer therapies

Novogen (ASX-NRT; NASDAQ-NVGN) is the ASX listed parent company of Novogen Research and Novogen Consumer Health, as well as a 78.1% and 81.3% holder of Marshall Edwards and Glycotex respectively. The core focus is on anti-cancer therapies. The lead product Phenoxodiol is currently being tested in a Phase III Clinical Trial. As well as Phenoxodiol, Marshall Edwards is also conducting Clinical Trials on NV-196.

The lead compound Phenoxodiol, has been granted FDA fast track status for chemotherapy refractory Ovarian Cancer and hormone refractory Prostate Cancer. Plus, the Phase III trial has FDA Special Protocol Assessment status.

The Ovation Trail

- To date, Phenoxodiol has completed a Phase II trial in combination with Cisplatin and separately with Paclitaxel. In these studies, the combination therapy reported a disease control rate of 76% and 74% on a patient pool of 21 and 19 respectively.
- These results allowed progression to a Phase III study, where 400mg tid of Phenoxodiol with weekly carboplatin will be trialled on about 400 subjects. The trial is being conducted on women with drug-resistant ovarian cancer. The anticipated primary end-point is an improvement in progression free survival.
- Interim data is expected to be released upon data collected on 95 subjects in mid-2008.
- The Phase III trial is anticipated to be conducted in 60 centres throughout Europe, Australia and the US.
- In November 2006, Marshall Edwards announced that the first patient entered the Phenoxodiol Phase III Clinical Trial, termed the Ovature Trial.
- The SPA process allowed for FDA evaluation of a clinical trial protocol and agree upon the end-points that would allow marketing registration.
- As a fast tracked Phase III study, Phenoxodiol will be eligible to apply for accelerated approval and priority review of the marketing application by the FDA for ovarian and prostate cancers.
- In October 2007, the first of the European Cohort were recruited into the Ovature Trial.

Recommendation

We estimated the value of Novogen to be US\$243 million (A\$277 million), although the valuation ranges US\$43 million on each side of US\$243m. The next revaluation trigger for the stock should be the release of the interim data on 95 patients. This is expected to be around mid-2008. The Phase III trial recruitment is anticipated to be completed around mid-late 2008, and full recruitment is required before the FDA can grant Fast Track approval should the Interim data prove statistically significant. It is at this point that Phenoxodiol could be approved by the FDA from marketing as an anti-cancer drug.

We recommend the company as a Speculative Buy, but we also recommend that investors wait for the share price to stabilise as the stock is on a clear downward trend. Novogen is an investment for the speculative investor, knowledgeable and tolerant of the inherent risks associated with investing into biotechnology investments.

Snapshot

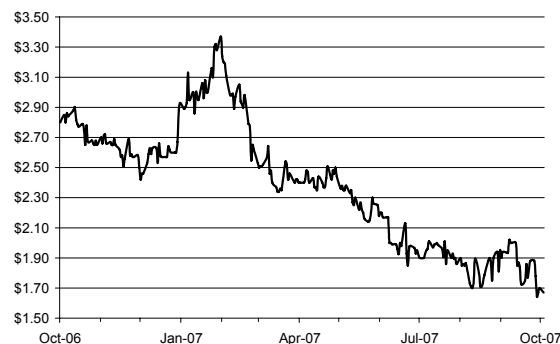
Last Price	\$1.67
Market Cap (A\$m)	A\$161m
52 Week High	\$3.49
52 Week Low	\$1.61
Sector	Pharmaceuticals - 352020

Investment Fundamentals

Year-end June	HY06	FY06	HY07	FY07
NPAT (\$m)	-6.5	-16.2	-10.6	-20.0
EPS (c)	-6.7	-16.7	-10.8	-20.5
% Change	NA	NA	NA	NA
DPS (c)	0.0	0.0	0.0	0.0
Franking (%)	0.0	0.0	0.0	0.0
Yield (%)	0.0	0.0	0.0	0.0
PER (x)	NA	NA	NA	NA

Source: Intersuisse Estimates

Price Chart



Business Description

Novogen is an international pharmaceutical company with expertise in the area of isoflavones and phenolic therapeutics and primarily dietary supplements. Novogen is targeting the treatment of cancer, heart disease, osteoporosis, Rheumatoid arthritis, Inflammatory Bowel Disease and Neurological and Autoimmune diseases.

Analyst: Darren J. Grubb PhD MBA

The Science of Phenoxodiol

Phenoxodiol is a pharmacophore of the naturally-occurring plant isoflavone, genistein. These plant hormones regulate plant cycle kinetics and death and may have similar effects in animals. The anti-cancer effect of isoflavones was initially suggested by the observation of an inverse relationship between dietary isoflavone intake and cancer incidence.

Genistein is an inhibitor of tyrosine kinases in human tumour cells and exerts modest anti-cancer activity against a wide range of human and animal cancers including melanoma, leukemias, breast cancer, gastrointestinal cancers, prostate cancer and other solid tumours.

Phenoxodiol is an analogue of genistein that delivers substantially greater anti-tumour potency and bioavailability. Although an active anti-tumour agent both *in vitro* and *in vivo* as a monotherapy, the drug is being developed in late-stage cancers as a chemo-sensitiser. *In vitro*, it shows a potent ability to restore sensitivity in tumour cells to platinum-based drugs and docetaxel where there is acquired resistance to such drugs.

The underlying mechanism of action of this chemo-sensitising effect is unclear, but may be associated with a reduction in sphingosine-1-phosphate levels and an increased degradation of anti-apoptotic proteins, with increased levels of both being linked to drug resistance in tumour cells¹.

Drug Resistance in Ovarian Cancer

The major limitation to the successful management of ovarian cancer is the development of resistance to the currently preferred chemotherapeutic regimen of carboplatin plus paclitaxel.

Chemotherapeutic drugs can trigger apoptosis and consequently the molecules involved in regulating apoptosis could be involved in drug resistance. One such molecule that has been implicated in drug resistance is the caspase inhibitor XIAP. In cells that are sensitive to the anti-drug, cisplatin down-regulates XIAP. In contrast, drug-resistant cells have shown no decrease in XIAP after exposure to cisplatin. Studies have identified that ectopic expression of XIAP can render cells more resistant to cisplatin. Conversely, antisense oligonucleotides directed to XIAP can sensitise resistant cells to cisplatin. These studies suggest that by preventing apoptosis, XIAP can potentially contribute to drug resistance².

Increased expression of XIAP has been shown to be associated with aggressive malignant behaviour and disease progression in a number of malignancies, including lymphoma, breast cancer, lung cancer and renal cell

carcinoma, as well as melanoma cell lines³. Phenoxodiol causes XIAP degradation and chemotherapy sensitisation in ovarian and other tumours.

Phenoxodiol's Potential

There are a number of investigational drugs and reformulations of existing drugs in Clinical Trials for the management of refractory ovarian cancer. However, the issue of refractory ovarian cancer continues to be an issue, with 1:10,000 US women succumbing to the disease per annum. Although the incidence of the cancer is declining, the mortality rate has remained static for the last 20 years.

Phenoxodiol's competitive advantage over reformulations or higher doses of existing drugs, is that evidence suggests that Phenoxodiol increased the sensitivity of existing Platinum based anti-cancer drugs. So, Phenoxodiol is likely to be complementary as opposed to being competitive to the incumbent conventional anti-cancer drugs.

- Phenoxodiol is likely to be an adjunct to conventional chemotherapy, there is more likely to be a dispensation for the oncologist to prescribe the drug in combination with incumbent chemotherapeutics with known clinical properties and profile. The Platinum drugs are generally effective at retarding cancer progression in susceptible cancers, so being able to revert a refractory tumour to become susceptible again extends the therapeutic regimes available to the oncologist.

In addition, it is known that dysfunction of one of a number of genes can cause or promote ovarian cancer. The table below illustrates the key compounds in development for each of these genes.

- Some of the investigational drugs in development that are targeting specific ovarian cancer associated genes are likely to enter the market and be very successful drugs. However, they would be only effective in patients with a dysfunction in the gene targeted. Should that gene not be the cause of the ovarian cancer, it is likely that such a drug would not impact the disease. Thus, as Phenoxodiol increases the utility of the platinum drugs, which are known to induce a response in the widest range of patients, it is likely that there would be a dispensation for the oncologist to extend the therapeutic regime of a suite of drugs that have the broadest patient population pool. Although Phenoxodiol's molecular target remains unknown and there is uncertainty on what percentage of the ovarian cancer drug refractory population would be responsive to Phenoxodiol's Platinum drug sensitising abilities. Novogen's Phase II trial implies that about 75% of ovarian cancer patients could benefit from Phenoxodiol.

The table below summarises the main drug in the market or development that target genes known to confer drug

¹ Annals of Oncology 17: 860-865, 2006, doi:10.1093/annonc/mdl010, Published online 8 March 2006

² Drug Resistance Updates 8 (2005) 311-321

³ Journal of Translational Medicine 2007, 5:6 doi:10.1186/1479-5876-5-6

resistance in ovarian cancers. Nevertheless, it is too early to accurately assess how any of the investigational drugs will perform should they enter the market or what percentage of the market share will be acquired.

Drugs and Investigational Drugs that are (or possibly) Useful for the Management of Drug Resistant Ovarian Cancer.

Name	Classification	Company	Gene Target	Status	Sales Revenue
AEG-35156	XIAP antisense	Aegera	XIAP	I	NA
NA	HGS-ETR1 & HGS-ETR2 antibody agonists	Human Genome Sciences, Cambridge Antibody Technology	TRAIL receptor	I/II	NA
GX-015-070	Small Molecule	Gemin X Biotechnologies	TRAIL receptor	I/II	NA
Oblimersen	Antisense Bcl-2	Genta	Bcl-2	III	NA
SPC-2996	Antisense Bcl-2	Santaris Pharma	Bcl-2	I/II	NA
Gleevec	Small Molecule	Novartis	Kit	Market	Global Sales US\$1.2bn (2006)
OSI-930	Small Molecule	OSI	Kit	I	NA
Herceptin	Antibody	Genentech	HER-2/ErbB2	Market	US Sales US\$1.2bn (2006)
Lapatinib	Mixed ErbB2 and EGF-R inhibitor	GSK	HER-2/ErbB2	III	NA
Canertinib	Inhibitor of all ErbB family	Pfizer	HER-2/ErbB2	II	NA
AZD-0530	Small Molecule	AstraZeneca	Src	I	NA
BMS-354825	Small Molecule	BristolMyersSquibb	Src	II	NA
AT-585	Akt inhibitor	Astex/ICR	Akt and PI 3-kinases	Preclinical	NA
PI-103	PI 3-kinase inhibitor	Piramed/ICR	Akt and PI 3-kinases	Preclinical	NA
Various	NA	Various	Akt and PI 3-kinases	Various	NA
17-AAG	Small Molecule	Kosan Biosciences / ICR / NCI	Akt and PI 3-kinases	II	NA
Atrasentan	Antagonist of the endothelin-A	Abbot	Endothelin-1 receptor	III	NA
MLN-120	Inhibitors of IKK—a NF _κ B activating kinase,	Millenium	NFκB	Preclinical	NA
Various	NA	Various	NFκB	Preclinical	NA
Decitabine	Reverses epigenetic silencing of <i>MLH1</i> gene by preventing methylation	Supergen & MGI Pharma)	MLH1	I	NA
Telcyta	Alkylating agent activated by GSTπ	Telik	GSTπ	III	NA
Phenoxodiol	target unknown, but drug induces apoptosis	Novogen	Unknown	II/III	NA

Modified from Drug Resistance Updates 8 (2005) 311–321, Drug resistance in ovarian cancer: The emerging importance of gene transcription and spatio-temporal regulation of resistance, A Richardson and SB Kaye.

The development status is listed according to clinical Phase I, II or III although many of these drugs are currently being pursued for indications other than ovarian cancer and the table is not indicative of the current status of these drugs in ovarian cancer. However, the data summarised indicates the drugs that could be useful in the treatment of drug-resistant ovarian cancer.

Marshall Edwards

Marshall Edwards (NASDAQ-GM MSHL) is the company which undertakes the Clinical Trials of compounds developed by Novogen. Almost all the value of the company resides in Phenoxodiol. It has no employees, as all operational activities are undertaken by Novogen under a service agreement. Marshall Edwards and Novogen share some directors, who are remunerated by both entities.

Marshall Edwards has a market capitalisation of US\$207 millions on a share price of US\$3.01 per share, with a price trading range of US\$2.21 to \$4.90 per share. Using an Options Model, we estimated the value of Marshall Edwards to be US\$262 million and conclude that the company is currently trading at the lower end of Fair Value.

Novogen is a 78.1% shareholder in Marshall Edwards, which supports the price as the company is thinly traded. The average and median daily volume turnover is 18,572 and 12,218 shares in the last 12 months.

In August 2007, a private placement to private equity investors raised US\$16.4m from the issuance of 5.464 million shares. In addition, the placement included warrants for 4 shares for each 10 shares subscribed at a strike price of US\$3.60 per share. The cash position of the end of June 2007 was US\$16.2 million, providing estimated current cash position of US\$28 million.

In June 2007, Marshall Edwards had contractual obligations for the conduct of clinical trials, pre-clinical research and development and manufacturing process development of US\$10.3 million. In addition, a further US\$8.0 million is payable to Novogen upon Approval of Phenoxodiol by the FDA or other regulatory authority.

NV-196 and NV-143

NV-196 is a synthetic anti-cancer compound developed by Novogen, based on an isoflavan ring structure. Preliminary screening studies NV-196 is in Phase I human testing and is being developed initially in oral form for the treatment of pancreatic and bile duct cancers.

NV-143 is currently in pre-clinical testing. Preliminary screening studies have identified broad anti-cancer activity against melanoma, glioma, prostate, ovarian, breast and lung cancer cells. NV-143 also exhibits broadly acting chemo-sensitising activity

Both of these drug candidates are analogues of Phenoxodiol, but exhibit different biological activity.

The first NV-196 Phase Ia study in three patients confirmed the bioavailability of the oral dosage form. That study showed that an oral dosing regimen had the potential to deliver therapeutically-relevant plasma levels of the drug, and that short-term therapy with NV-196 was well tolerated. NV-196 has also completed a second Phase Ia safety and

pharmacokinetic study in nine patients at the Brisbane Mater Hospital.

NV-143 is still undergoing pre-clinical evaluation for determination of its potential in the treatment of malignant melanoma and is not expected to enter clinical trials until the results of pre-clinical testing are complete.

Glycotex

Novogen has an 81.3% stake in the private US entity, Glycotex. Glycotex focuses on development of wound management products.

In February 2007, Glycotex raised US\$1.6 million from private equity for 3.6% of the company.

The operations of Glycotex are opaque. Novogen and Glycotex share some directors, who are remunerated by both entities. The company states that Glycotex has Glyc-101 in Phase II clinical trials from wound management.

Novogen Valuation

We estimated the value of Novogen to be US\$243 million (A\$277 million), although the valuation ranges US\$43 million on each side of US\$243m.

This represents a currently fully diluted share price of A\$2.79 per share or a 41% discount to the current share price.

The valuation is composed of the

- Holding of Marshall Edwards, calculated at US\$192 million (A\$219 million).
- The collective value of the earlier stage clinical trial programmes, estimated at to be worth US\$51 million (A\$58 million).

This assumes that all cash is injected into operational development, plus the probability of success and the expected returns are based on the average of all cancer drugs launched after 1996.

The next revaluation trigger for the stock should be the release of the interim data on 95 patients. This is expected to be around mid-2008. The final patient recruited into the Phase III trial is anticipated to be completed around mid-late 2008. Full recruitment is required before the FDA can grant Fast Track approval should the Interim data prove statistically significant.

We recommend the company as a Speculative Buy, but we also recommend that investors wait for the share price to stabilise as the stock is on a clear downward trend.

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