

19 May 2010

## **ANP to present to Isis Shareholders in the US**

Antisense Therapeutics Ltd. (ANP) Managing Director, Mark Diamond, will give a poster presentation at Isis Pharmaceuticals Inc. (NASDAQ: ISIS) Annual Stockholders Meeting on Wednesday 2 June 2010 in the United States.

Isis is a major shareholder and technology partner of ANP.

Full presentation follows.

**Antisense Therapeutics Limited** (ASX: ANP) is an Australian publicly listed biopharmaceutical drug discovery and development company. Its mission is to create, develop and commercialise antisense pharmaceuticals for large unmet markets. ANP has two drugs in development and two drugs in pre-clinical research. ATL1102 (injection) has successfully completed a Phase II efficacy and safety trial, significantly reducing the number of MRI lesions in patients with multiple sclerosis. ATL1103 is a second-generation antisense drug designed to lower blood IGF-I levels and is entering the clinical stage of development as a potential treatment for growth and vision disorders. ATL1102 (inhaled) is at the pre-clinical research stage as a potential treatment for asthma. ATL1101 is a second-generation antisense drug at the pre-clinical stage being investigated as a potential treatment for prostate cancer

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**Isis Pharmaceuticals Inc. Annual Meeting**

**2 June 2010**

**Antisense Therapeutics Ltd  
Melbourne, Australia  
ASX: ANP**

## **Forward Looking Statements**

This presentation contains forward-looking statements regarding the company's business and the therapeutic and commercial potential of its technologies and products in development. Any statement describing the company's goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those risks or uncertainties inherent in the process of developing technology and in the process of discovering, developing and commercialising drugs that can be proven to be safe and effective for use as human therapeutics, and in the endeavour of building a business around such products and services. Actual results could differ materially from those discussed in this presentation. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in the Antisense Therapeutics Limited Annual Report for the year ended 30 June 2009 and the Half Year Report of 31 December 2009, copies of which are available from the company or at [www.antisense.com.au](http://www.antisense.com.au).



## The Opportunity

Multiple project assets to commercially exploit and to progress to build value

- *ATL1103 for growth and sight disorders – move into clinical trials*
- *ATL1101 for prostate cancer - ready to move into clinical trials. Look to partner*
- *ATL1102 for multiple sclerosis - confirm potential for further development and/or out-licensing*
- *ATL1102 inhaled asthma – confirm development/partnering strategy*

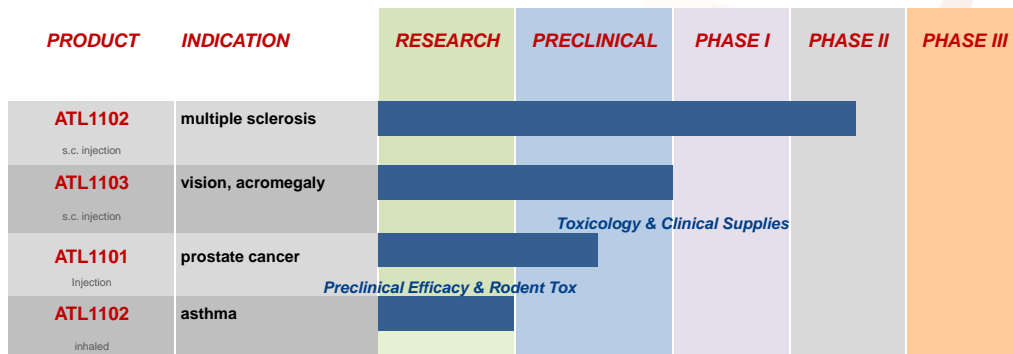


## Business Strategy

- Continue to leverage collaboration with Isis Pharmaceuticals
- Utilise world-wide exclusive licenses which cover the targets for all relevant applications
- Grow pipeline of antisense compounds for large unmet markets & niche indications
- Use technology know-how & expertise to fast-track project development in cost effective manner
- Realise value of all assets through successful development, partnering and commercialization



## Product Research & Development Pipeline



All pipeline drugs and 2<sup>nd</sup> generation antisense compounds derived via Isis collaboration



## ATL1102 for Multiple Sclerosis

### Disease & Market

- Life-long chronic disease of the central nervous system
- Global drug sales of >US\$6bn and forecast to grow to US\$10bn by 2012
- Need for more effective drug with less side effects

### Product

- 2nd generation antisense inhibitor of VLA-4 protein
- VLA-4 is a clinically validated target in MS
- Successful Phase IIa trial confirming drug activity and safety in MS patients

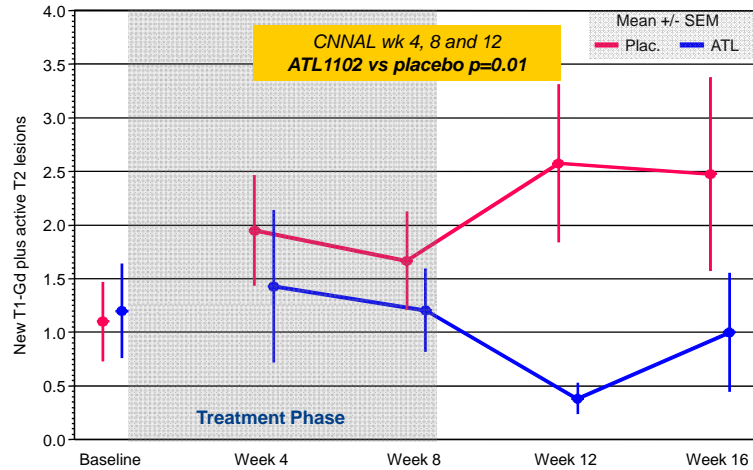
### Project status

- Company assessing development options



## Phase II study met primary end-point: reduction in new active lesions

ATL1102 reduced no. of new active lesions by 54.4%, p = 0.01

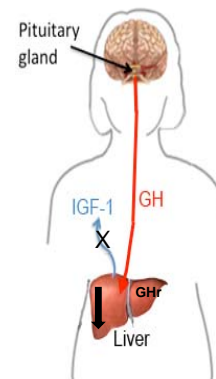


## ATL1103 for growth & sight disorders

- Antisense inhibitor to the Growth Hormone receptor (GHR)
  - **Acromegalics** have elevated levels of both serum GH and IGF-I
  - $\checkmark$  serum IGF-I is associated with clinical improvement in **retinopathy**
- **ATL1103** inhibits GHR production in the liver which reduces GH binding to GHR thereby reducing IGF-I production and secretion by the liver into the blood (serum)

**ATL1103 reduces liver GHR & blocks GH action on the liver**

**reducing IGF-I in blood**



adapted from [neurosurgery.ucla.edu/body.cfm?id=1](http://neurosurgery.ucla.edu/body.cfm?id=1)

## ATL1103 for Growth & Sight Disorders: Market

### Growth - Acromegaly

- A disorder of excess growth hormone in adults associated with excess serum IGF-I
- Orphan drug indication - affects >40,000 people (US, Europe and Japan)
- High treatment costs (up to A\$30K/annum)
- Somatostatin agonists market leader
  - *Effective in ~ 60% of patients in normalizing serum IGF-I*
  - *Sales approaching \$1Billion*
- Somavert® (pegvisomant) GHR antagonist (same target as ATL1103)
  - *Effective in > 90% of patients in normalizing serum IGF-I*
  - *Limited use as more expensive (up to and greater than A\$60K/annum) and inconvenient administration and dosing regimen (e.g. daily injection)*



## ATL1103 for Growth & Sight Disorders: Market

### Sight - Diabetic Retinopathy

- Disorder of the retina of the eye caused by diabetes potentially leading to blindness
- High prevalence: over 5 million Americans affected by diabetic retinopathy
- Advanced (proliferative) form of diabetic retinopathy characterized by neovascularisation (new blood vessels) in the retina
- No approved drug treatments for the advanced form
- Potential multi \$Billion market



## Pipeline: ATL1103 for growth & sight disorders

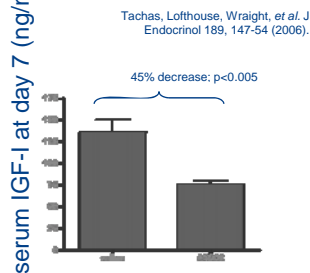
### Activity of GHR antisense confirmed in animal models

- Successfully suppressed circulating IGF-I levels in mice and primates
- Significantly reduced retinal neo-vascularisation (new blood vessels) in mouse animal model of retinopathy  
*Wilkinson-Berka, Lofthouse, Jaworski, Ninkovic, Tachas, Wraight: Mol Vis 13, 1529-38 (2007)*
- Data on suppression of circulating IGF-1 levels in mice published in peer reviewed scientific journal  
*Tachas, Lofthouse, Wraight, et al.: J Endocrinol 189, 147-54 (2006)*

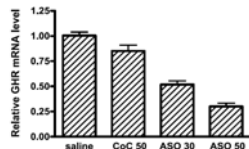


## ATL1103 pre-clinical mouse pharmacology

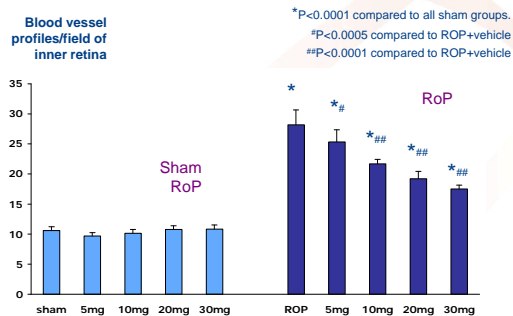
### IGF-I suppression



### GHR mRNA target inhibition



### Inhibition of retinal neovascularisation



ATL227446 dose / kg body weight, i.p.

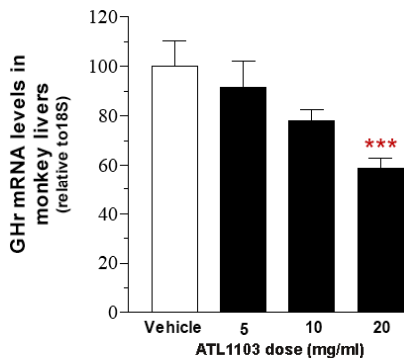
Presented at EASD 41st Annual Meeting, Athens, September 2005



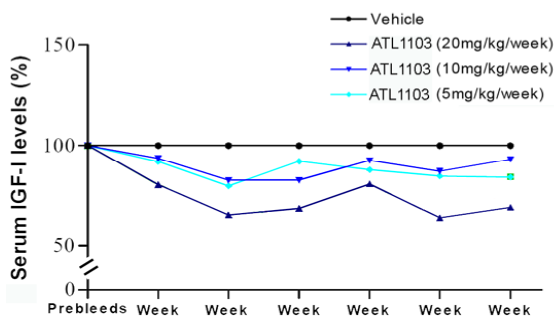
## ATL1103 active in primates

- Significant suppression of hepatic target mRNA
- Pharmacologically relevant suppression of circulating IGF-I
- Therapeutic paradigm demonstrated in non human primates

Hepatic GHR mRNA levels



Mean IGF-I level (vehicle normalised % baseline)



Antisense Therapeutics Ltd, unpublished data on file



## ATL1103 for growth & sight disorders

### Key features of ATL1103 development program

- GHR target is clinically validated in acromegaly (Somavert® – pegvisomant)
- GHR is expressed in liver which is a target organ for antisense drug distribution
- Ability to test for drug activity (serum IGF-I is clinical endpoint ) in early human studies
- Limited competition
- Anticipate similar high level of efficacy to GHR targeting drug Somavert® with potential advantages over Somavert® including dosing, administration and cost

### Project status

- Successfully completed toxicology studies
- Anticipate submitting application to conduct clinical trial 2<sup>nd</sup> Half 2010



## ATL1101 for Prostate Cancer

Second most frequently diagnosed cancer in men after skin cancer

- $\approx$  1 in 6 men will develop prostate cancer
- $\approx$  1/3 to 1/2 recur after local treatment, risk progression to metastatic prostate cancer

Metastatic prostate cancer initially responds to androgen (hormone) ablation therapy

- Disease gradually progresses to hormone refractory or metastatic castrate resistant prostate cancer (mCRPC)
- mCRPC is most dangerous and aggressive form
- Treatment options are limited and prognosis is poor

mCRPC treatment options

- Depend on disease severity
- Include radiation and chemotherapy (e.g. docetaxel), which are designed to induce programmed cell death (apoptosis) of tumour cells
- There is a pressing need for the development of new treatment options



## ATL1101 targets IGF-IR : Enhancing tumour kill

New targeted therapy approaches aim to

- enhance effect of androgen ablation on induction of tumour cell apoptosis when disease is still androgen dependent
- delay progression to mCRPC
- mCRPC: enhance effect of cytotoxic therapies, e.g. Taxotere® (docetaxel)

IGF-IR is an emerging therapeutic target in oncology

- IGF-IR signalling up-regulated in androgen resistance
- IGF-IR inhibition blocks key cell survival and proliferation signalling pathways MAPK & PI3K/AKT
- IGF-IR inhibition sensitises tumour cells to docetaxel-induced apoptosis



## ATL1101 targets IGF-IR: High Interest Area in Oncology

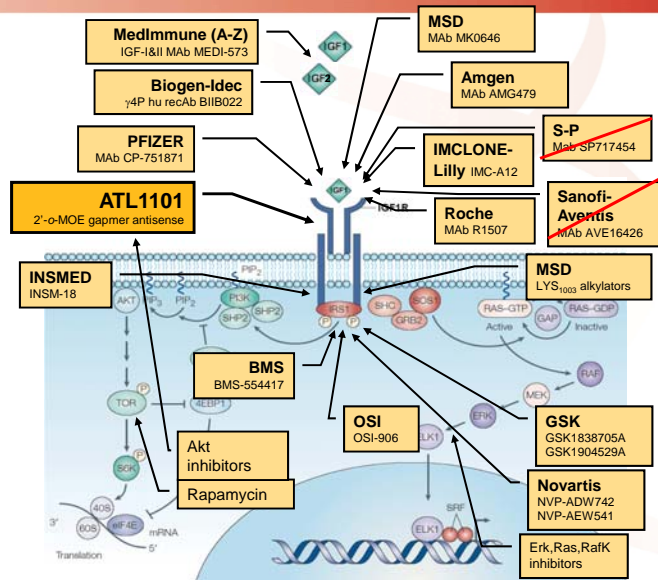
- Monoclonal antibodies, Kinase inhibitors & SMI antagonist strategies have receptor specificity & other challenges

- ATL1101 is designed to specifically block IGF-IR synthesis & inhibit downstream signalling

- ATL1101 also blocks IGF-IR:IR hybrid receptors

<sup>1</sup> Frasca et al. *Arch Physiol Biochem* 114, 23-37 (2008)

<sup>2</sup> Zhang et al. *Cancer Res* 67, 391-7 (2007)



adapted from Pollak et al., 2004 *Nature Reviews (Cancer)* 4: 505



## ATL1101 for Prostate Cancer

### Product

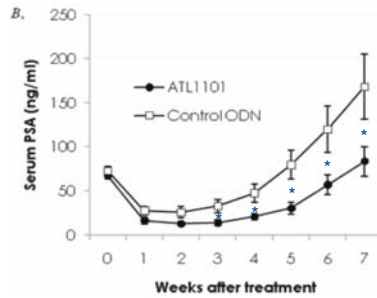
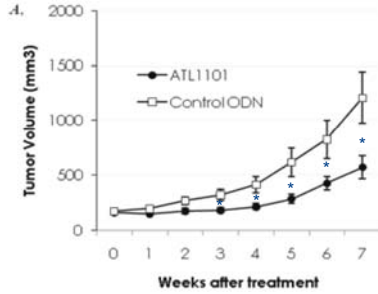
- ATL1101 is a 2nd generation antisense inhibitor of IGF-IR

### Project status

- ATL1101 has shown robust preclinical pharmacology
  - *Potent suppression of key tumour signalling pathways & prostate cancer tumour growth*
- Select toxicology studies completed that would support clinical trial in prostate cancer patients

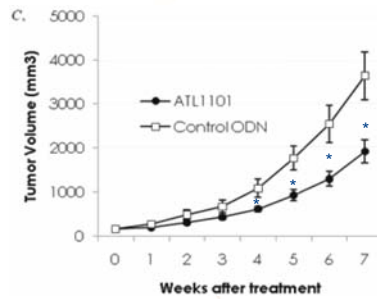


## ATL1101 systemic delivery: Effects on LNCaP and PC-3 tumours *in vivo*

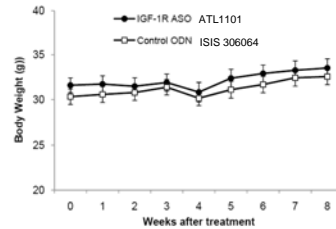
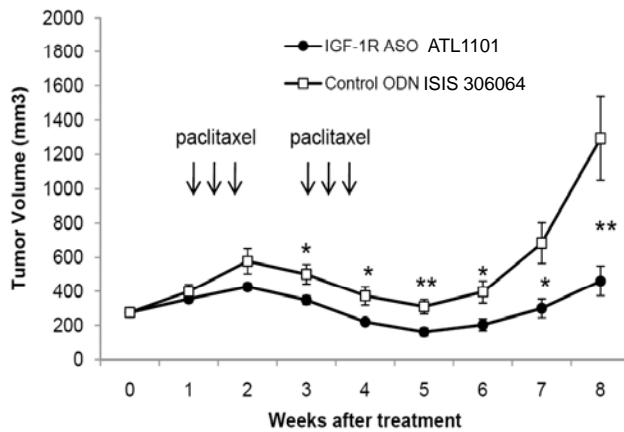


A, LNCaP cells were inoculated s.c. and when PSA values exceeded 50 ng/ml, mice were castrated and randomly selected for treatment with ATL1101 or control ODN (15 mg/kg) injected i.p. once daily for 7 days and 3 times per week thereafter. B, blood samples were obtained from the tail vein of the mice once weekly to measure serum PSA by ELISA. C, PC-3 cells were inoculated s.c. and when tumors reached 100 mm<sup>3</sup>, mice were randomly selected for treatment with the same protocol as LNCaP. Each point represents the mean tumor volume in each group containing 10 mice; bars, SE. \* differs from control ODN treatment group ( $p < 0.05$ ) by Student's t test.

In LNCaP xenografts, ATL1101 significantly delayed the tumor growth and PSA rise rates after castration.  
In PC3 xenografts, ATL1101 monotherapy significantly reduced tumor volume compared to the mice treated with control ODN (ISIS306064).



## ATL1101 enhances Taxol<sup>®</sup> tumour cell cytotoxicity *in vivo*



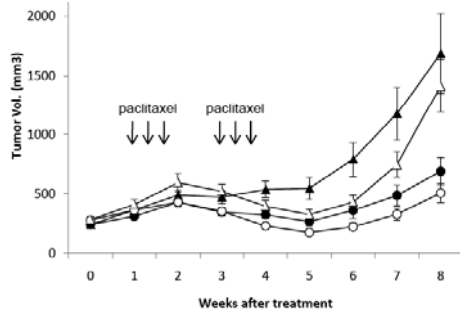
### Combination therapy ATL1101 and Paclitaxel

For *in vivo* study,  $2 \times 10^6$  PC-3 cells were inoculated s.c. in the flank region of 6-8 week-old male athymic nude mice via a 27-gauge needle under methoxyfluorane anesthesia. When mice bearing PC-3 tumors reached a palpable tumor volume of 200 mm<sup>3</sup> they were randomly assigned for treatment with 15 mg/kg IGF-1R ASO (ATL1101) or mismatched ODN(ISIS306064) once daily for 5 days and three times per week thereafter by i.p. injection. At days 7, 9, 11 and 21, 23, 25, 0.5 mg of micellar paclitaxel was administered i.v. once daily. Each experimental group consisted of 10 mice.

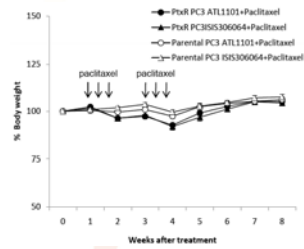


Furukawa, Wraight, Monia, Gleave & Cox (2009), presented at 10th National Prostate Cancer Symposium, Melbourne, Australia

## ATL1101 activity in taxane-resistant prostate cancer cells: ATL1101 retains cytotoxicity & re-sensitises to Taxol® effects *in vivo*



For *in vivo* xenograft studies,  $2 \times 10^6$  either parental PC3 or PtxR PC3 cells were inoculated s.c. in the flank of 6-8 week-old male athymic nude mice. When tumors reached 200 mm<sup>3</sup>, mice were randomly selected for treatment with 15 mg/kg ATL1101 or control oligonucleotide (ISIS 306064) injected i.p. once daily for 7 days and 3 times per week thereafter. For combination setting with paclitaxel, at days 7, 9, 11 and 21, 23, 25: 0.5 mg of paclitaxel was administered i.v. once daily. Each experimental group consisted of 10 or 11 mice. Tumor volume measurements were performed once weekly.



Antisense Therapeutics Ltd. proprietary data on file

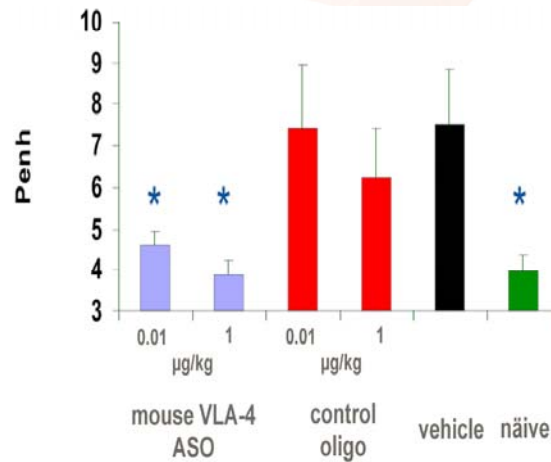


## Inhaled ATL1102 for Asthma

**Product:** Inhaled VLA-4 antisense

- Positive effects demonstrated in acute asthma model (mouse)
- Drug active at low inhaled doses
- Key asthma indicators suppressed
  - airway hyperresponsiveness
  - lung eosinophilia

Sub- $\mu$ g/kg inhaled doses of mouse VLA-4 antisense drug ("ASO") suppress OVA-induced airway hyperresponsiveness compared to control oligonucleotide drug ("control oligo")



\*P ≤ 0.05 vs. Vehicle



## ANP – Looking Forward

- ATL1103 for growth and sight disorders - intend to move into clinical development
  - *Submission of clinical trial application anticipated 2'H'2010*
- ATL1101 for prostate cancer
  - *Intention to out-license/move into clinical development*
- ATL1102 for MS and asthma
  - *Receive back data etc from Teva on MS opportunity and confirm next steps (e.g. Partner, Develop or Hold)*
  - *Look to out-license ATL1102 for asthma*