



# ANTISENSE THERAPEUTICS

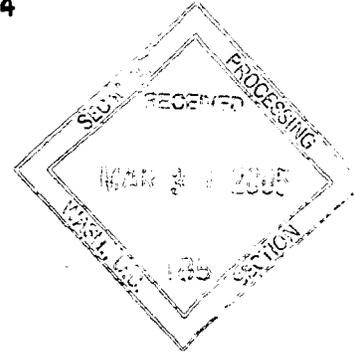
22 March 2005



05006984

Securities and Exchange Commission  
 Judiciary Plaza  
 450 Fifth Street  
 Washington DC 20549  
 UNITED STATES OF AMERICA

SUPPLE



Dear Sir/Madam

**Re: Antisense Therapeutics Limited**

Please find attached a copy of the following announcement lodged with the Australian Stock Exchange (ASX):

Date of Announcement/Lodgement	To:	Title	No of pages
21 March 2005	ASX	Asthma Data on Inhaled Antisense Drug to be Presented at Respiratory Medicine Conference	9

Yours sincerely

*N. Korchev*

Natalie Korchev  
**Company Secretary**

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## ANTISENSE THERAPEUTICS

21 March 2005

The Companies Section  
The Australian Stock Exchange Limited  
530 Collins Street  
MELBOURNE VIC 3000

### ASTHMA DATA ON INHALED ANTISENSE DRUG TO BE PRESENTED AT RESPIRATORY MEDICINE CONFERENCE

Today, Antisense Therapeutics Limited will be presenting asthma data from animal studies using an inhaled form of an antisense drug to VLA-4. Research Manager Dr Shari Lofthouse will give an oral presentation at the Annual Scientific Meeting of the Thoracic Society of Australia and New Zealand, entitled "Aerosol delivery of VLA-4 Specific Antisense Oligonucleotides Inhibit Airway Inflammation and Hyperresponsiveness in Mice". A copy of the presentation slides is attached.

Antisense Therapeutics' most advanced drug is ATL1102, a second generation antisense inhibitor targeting the VLA-4 protein. VLA-4 is an immune cell adhesion molecule thought to be involved in the inflammatory process in diseases like asthma. In December 2004, the company announced that it had generated encouraging data in one of the most widely used experimental models of asthma, the ovalbumin-challenged mouse model.

The key points of today's presentation are

- the VLA-4 antisense drug suppressed lung airway hyperresponsiveness at very low inhaled doses
- the inhaled drug was effective in inhibiting the accumulation of eosinophils (immune cells known to be major effectors in asthmatic attacks) in the lung
- the inhaled drug inhibited airway mucus accumulation

"We are pleased to have had this data accepted for presentation at a significant thoracic medicine forum. Our animal data encourages us to explore the potential of ATL1102 as an inhaled therapy for asthma, a highly debilitating and increasingly prevalent disease", said Antisense Research Director, Dr Christopher Wraight.

#### Background Information

*Asthma* is a chronic lung condition characterised by periodic episodes of airway inflammation and constriction resulting in wheezing, coughing, chest tightness and shortness of breath. The episodes typically occur in response to stimuli such as allergens, chemical irritants or low temperatures. Up to 1 in 4 children, and 1 in 10 adults will experience asthma symptoms at some time in their lives.

*ATL1102* is a second generation antisense inhibitor of CD49d, a subunit of VLA-4 (Very Late Antigen-4), and is currently in development as a treatment for MS. In inflammation, white blood cells (leukocytes) move out of the bloodstream into the inflamed tissue, for example, the CNS in MS, and the lung airways in asthma. The inhibition of VLA-4 may prevent white blood cells from entering sites of inflammation, thereby halting progression of the disease. Inhibition of VLA-4 in animals has demonstrated positive effects on a number of inflammatory diseases such as MS. Several other VLA-4 inhibitors are in clinical development for inflammatory conditions.

**About Antisense Therapeutics Limited**

Antisense Therapeutics Limited (ASX: ANP) is an Australian publicly listed biopharmaceutical drug discovery and development company. ANP's mission is to create, develop and commercialise novel antisense pharmaceuticals for large unmet markets. Its two most advanced projects target Multiple Sclerosis (ATL1102), and Psoriasis (ATL1101).

ANP plans to commercialise its pipeline via licensing/collaboration agreements with major biotechnology and pharmaceutical companies.

ANP's major shareholders include Circadian Technologies Limited (ASX: CIR), Isis Pharmaceuticals Inc (NASDAQ: ISIS) and Queensland Investment Corporation.

**Contact Information:**

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Company Secretary – Natalie Korchev +61 3 9827 8999

**Aerosol delivery of VLA-4 specific antisense oligonucleotide inhibits airway inflammation and hyperresponsiveness in mice**

Shari Lofthouse, Jeffrey Crosby, David Tung, Doreen Miller, Kelly McKay, George Tachas, Christopher Wraight, James Karras and Susan Gregory



ANTISENSE THERAPEUTICS



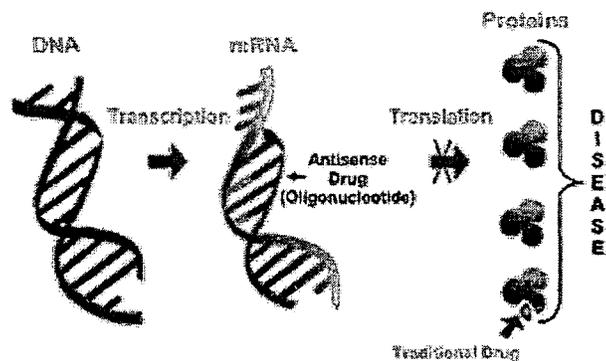
TSANZ Annual Scientific Meeting March 2005

**VLA-4 in asthma**

- VLA-4 is the  $\alpha_4\beta_1$  integrin (CD49d/CD29)
- Mediates binding of cells to VCAM-1 & fibronectin; primarily T cells and eosinophils in asthma
- Participates in cell adhesion, cell trafficking and cell activation
- VLA-4 inhibitors (Abs, small molecules) have been tested in asthma models with varying results



## Antisense: mRNA is the pharmacological target



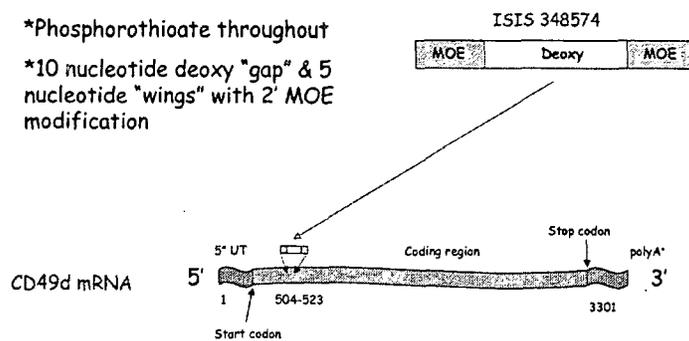
ISIS  
PHARMACEUTICALS

## 2<sup>nd</sup> generation antisense oligonucleotide to VLA4

2<sup>nd</sup> generation antisense chemistry provides enhanced stability, affinity and safety;

\*Phosphorothioate throughout

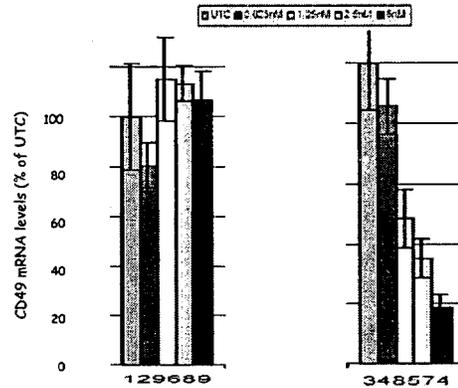
\*10 nucleotide deoxy "gap" & 5 nucleotide "wings" with 2' MOE modification



## ISIS 348574 reduces CD49d mRNA level in vitro

Dose response analysis of ASO to CD49d (348574) and a random oligonucleotide control (129689) in b.END cells

Dose Response Analysis of Lead ASOs to Mouse CD49d in b.END cells



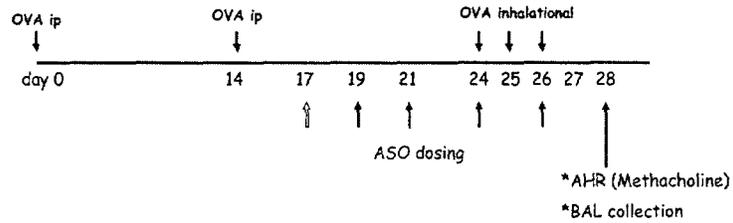
ISIS

## Aims

- To study the effect of an antisense oligonucleotide directed against the CD49d chain of VLA-4 in a mouse model of asthma
  - ASO is delivered by inhalation
  - OVA mouse model is used; parameters include;
    - AHR (Methacholine induced)
    - Eosinophilia (bronchial alveolar lavage)
    - Mucus (goblet) cell number in airways



## Methods



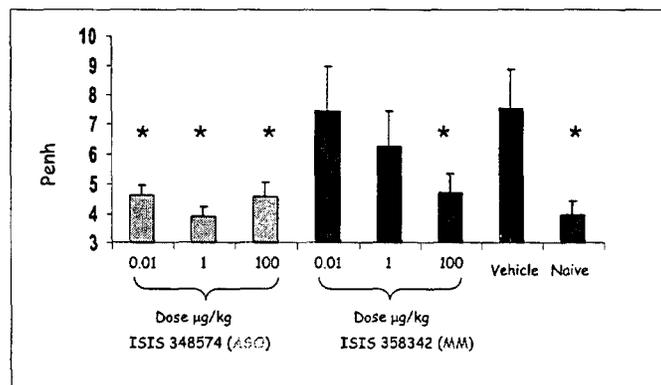
### Treatment Groups n=10 per group

- Vehicle (saline); OVA sensitised
- Negative control; naïve mice -unsensitised to OVA
- ASO (ISIS 348574) at 3 doses (0.01 to 100µg/kg); OVA sensitised
- Mismatch oligonucleotide (ISIS 358342) at 3 doses (0.01 to 100µg/kg); OVA sensitised



## Airway Hypersensitivity

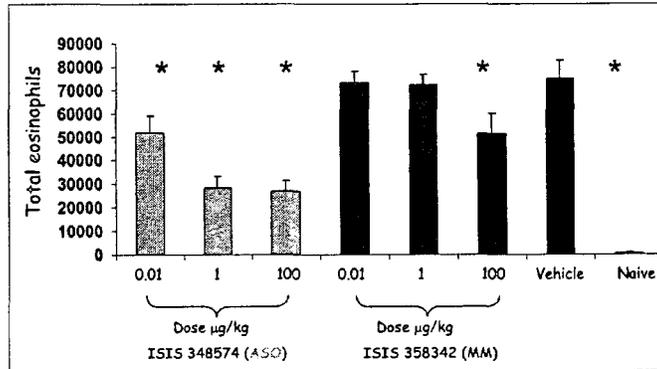
Effect of inhaled VLA4 antisense vs. mismatch control on the Penh response to methacholine (100 mg/ml) in OVA-challenged mice



\* p<0.05 compared to vehicle

## Eosinophilia

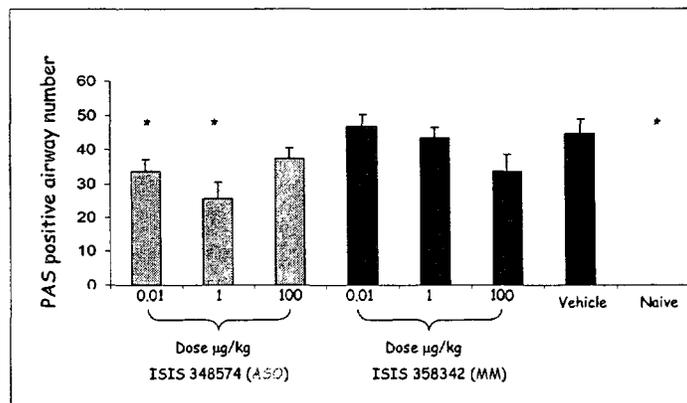
Effect of inhaled VLA-4 antisense vs. a mismatch control on the total eosinophil count in airways of OVA-challenged mice



\* p<0.05 compared to vehicle

## Mucus (goblet) cells in airways

Effect of inhaled VLA-4 antisense vs. a mismatch control on the total number of PAS positive (mucus-secreting) airways of OVA-challenged mice

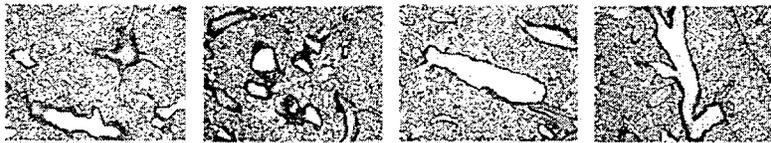


\* p<0.05 compared to vehicle

## VLA-4 Histology



Vehicle treated



ASO-treated 1ug/kg

Any airway with PAS positive cell is scored as a positive



## Summary

- The 2<sup>nd</sup> generation antisense oligonucleotide ISIS 348574, targeting the CD49d chain of VLA-4;
  - Decreases airway hypersensitivity - up to ~80%
  - Decreases eosinophilia - up to ~60%
  - Decreases mucus + airways - up to ~37%

when delivered via the aerosol route at a low dose  
in the mouse OVA model of asthma



## Conclusion

*Inhaled antisense to VLA-4 has the potential for therapeutic use in asthma and warrants further investigation*

A human 2<sup>nd</sup> generation antisense drug (ATL1102) against VLA-4 is currently in development. Toxicology studies, and a Phase I clinical trial (sc route) have been completed for ATL1102.

