ATL1103 for Cancer and Diabetic Complications

ASX:ANP
Rationale for ATL1103 for Cancer and Diabetic Complications

- ATL1103 is a clinically advanced drug that targets the Growth Hormone receptor (GHR)
- Inhibits GHR production in the liver thereby reducing IGF-I in the blood (sIGF-I)
- Reducing GH effects and sIGF-I has a potential role in the treatment of a number of diseases including Acromegaly, Cancer, Diabetic Retinopathy and Nephropathy
- Development of ATL1103 for Acromegaly/Endocrinology partnered with Cortendo, however ANP retains world-wide rights for all other indications (e.g. cancer and diabetic complications)
- Existing ATL1103 toxicology and clinical data would support and expedite future patient trials in these new indications reducing the time and cost for moving into Phase II
- Patents granted to 2024/2025 with potential for up to 5 years extension
- Company reviewing the multiple ATL1103 value adding opportunities and expects to report on plans in the coming months
ATL1103 – Antisense Drug to the Growth Hormone receptor

- 2nd generation antisense inhibitor to the Growth Hormone receptor (GHR)
- 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
- IGF-I has a role in the pathogenesis of acromegaly, diabetic retinopathy, nephropathy and certain cancers
- ↓ sIGF-I is associated with clinical improvement in these multiple disease indications

ATL1103 reduces liver GHR & blocks GH action on the liver

Reducing IGF-I in blood

Adapted from neurosurgery.ucla.edu/body.cfm?id=101
ATL1103 in Cancer

- Cancer is a disease associated with abnormal cell survival, growth, motility and adhesion and the insulin-like growth factor (IGF-I) plays an important role\textsuperscript{1}

- Lower sIGF-I protects against the risk of prostate, breast, lung & colon cancer

  - Men with prostate cancer in the highest quartile of IGF-I levels had a higher risk than men in the other quartiles\textsuperscript{2}

- Reduction of sIGF-I using a GHR antagonist decreased tumour volume in breast cancer in animal models and helped in reducing colon cancer and liver metastasis in animals\textsuperscript{3}

- Surgical removal of the pituitary (which reduces GH and sIGF-I) has shown clinical benefit in the treatment of both prostate and breast cancer patients\textsuperscript{4}

\textsuperscript{1} Brahmkhatri VP et al, Biomed Res Int 2015
\textsuperscript{2} Renehan AT et al Lancet 2004 24; 363 (9418): 1346-53
\textsuperscript{3} Waters & Barclay Endocrinology 148, 10: 4533-35 (2007) and
\textsuperscript{4} Pearson OH et al Cancer Research 1978, 38, 4323
ATL1103 target (GHR) role in Cancer Prevention

- Reductions in GH and IGF-I signalling appear to be important in protecting against development of cancer (Gallagher and LeRoith Cell Metab 13 April 6 2011)

  - 99 subjects with Laron syndrome (GHR deficiency) studied over 22 years
    - Subjects experienced only 1 case of cancer (non lethal) vs 17% of the control population (relatives without the syndrome)
    - No cases of diabetes were observed compared to 5% in the control population
  - Serum from the 99 subjects was tested in vitro and showed decreased cell proliferation potential and reduced expression of pro-growth signalling and induced higher apoptotic activity, thereby potentially protecting cells from cancer
  - Authors conclude ‘it is worth considering testing medications that block GH activity in ways that protect against diseases of ageing, in particular cancer’
ATL1103 for Cancer Treatment (Breast)

• Breast cancer is the 3rd most prevalent cancer in the developed world
• Multi Billion dollar sales for drugs currently used to treat breast cancer
• Breast cancer rates are increased 2-fold in premenopausal women in the high end of the normal range of sIGF-I
• ATL1103 mechanism of action in (breast) cancer treatment is supported and validated by:
  o Data showing ATL1103 reductions in GHR in a human breast cancer cell line, and reductions in GHR and sIGF-I in mouse, primate and human studies
  o Elevated GHR expression observed in human breast cancer tissues
  o Reduction of sIGF-I using GHR antagonist decreased breast cancer volume in animal models
  o Surgical removal of the pituitary (which reduces sIGF-I and GH) in breast cancer patients who respond to, or are resistant to tamoxifen (breast cancer treatment), produced remissions of an average of 11 months, and in some patients extended life from 5.6 to 25.8 months

1 Renehan AG et al Lancet 2004, 363: 1346-1353
2 Pearson OH et al Cancer Research 1978, 38, 432
ATL1103 for Diabetic Retinopathy

- Diabetic retinopathy (DR) is a disease of the retina caused by diabetes and comes in 2 main forms, non proliferative and the more advanced proliferative form (PDR).

- In PDR, new blood vessels form and leak blood; oedema and retinal thickening can also present blocking light reaching the retina thereby potentially causing blindness.

- DR is the leading cause of blindness with ~23,000 cases of blindness per year. Approx. 300,000 in US and Europe have PDR.

- No approved drugs for advanced PDR – considered a multi billion dollar opportunity.

- ATL1103 mechanism of action in diabetic retinopathy is supported and validated by:
  - ANP animal data where an antisense to GHR reduced retinal neo-vascularisation (new blood vessels) in a mouse model of retinopathy.
  - Irradiation /ablation of the pituitary gland (which decreases GH and sIGF-I) reduced the number of blood vessels in the retina of patients and increased their visual acuity.
  - Somatostatin analogues (that also reduce GH and sIGF-I) such as octreotide provided clinical benefit in Phase II and III studies.
ATL1103 for Diabetic Nephropathy

- Diabetic nephropathy (DN) is a progressive disease of the kidney glomerulus caused by high blood sugar
- About 40% of type II diabetics have DN and 6 million patients in the US, Europe and Japan have clinically significant forms of the disease
- Both sIGF-I and local kidney GH/IGF-I have roles in the pathogenesis of DN
- Despite treatment there is deterioration of renal function and this unmet medical need is considered a multi-billion dollar opportunity
- ATL1103 mechanism of action in DN is supported and validated by:
  - Data showing ATL1103 reduces GHr and IGF-I in the kidney in primates, and reduces GHr (GHBP) and sIGF-I in normal volunteer and acromegaly patient studies
  - Treatments that reduce GHr and sIGF-I have demonstrated positive effects in mouse models and have shown benefits in studies in diabetic nephropathy patients