ATL1103 for Cancer and Diabetic Complications

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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

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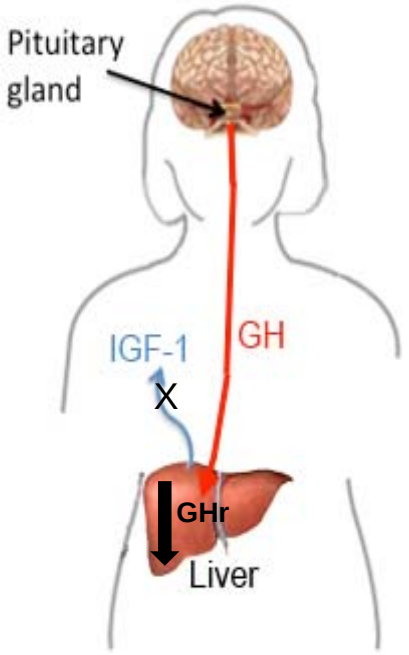
ATL1103 – Antisense Drug to the Growth Hormone receptor

- 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

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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[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[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[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[4]

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

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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)
- GHr deficiency is associated with major reduction in pro-aging signaling, cancer and diabetes in humans (Guevera-Aguirre, Cohen, et al Sci Transl Med 3. Feb (2011); Vol3 Issue 70ra 13)
  - 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’

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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[1]
- ATL1103 mechanism of action in (breast) cancer treatment is supported and validated by:
  - 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
  - Elevated GHr expression observed in human breast cancer tissues
  - Reduction of sIGF-I using GHr antagonist decreased breast cancer volume in animal models
  - 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[2], and in some patients extended life from 5.6 to 25.8 months[3]

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1 Renehan AG et al Lancet 2004, 363: 1346-1353
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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

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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

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