N4 Pharma plc

N4 Pharma has appointed Dr Alastair Smith as an independent Non-Executive Director ('NED') of the Group with immediate effect. Alastair is the founder and former Chief Executive Officer of Avacta Group plc (AIM: AVCT, 'Avacta'), the clinical-stage biotech focussed on oncology and advancement of its pre|CISION™ tumour targeting platform. Obvious parallels between the two businesses, including the building of therapeutic pipelines that are strongly differentiated by proprietary technologies with opportunity for early commercialisation through licensing, suggest his extensive/related scientific experience plus widespread industry contacts will provide valuable support to N4P when progressing its ambition to make Nuvec® a delivery platform of choice for the gene therapy industry. Dr Smith joins N4P's remuneration and audit committees. Today's release also confirmed Technical Director, David Templeton, has retired with immediate effect due to personal reasons.

Dr Alastair Smith – Highly experienced early-stage biotech CEO

Founded and incorporated back in 2005, Dr Smith advanced Avacta's development of AVA6000, a peptide drug conjugate form of doxorubicin (to which it acquired the rights in 2018), through Phase 1a clinical trials for local treatment of advanced or metastatic solid tumours. The underlying pre|CISION™ platform technology has been shown by AVA6000 to dramatically reduce the toxic side effects of the chemotherapy potentially opening the opportunity to a range of safer and better tolerated cancer therapies. Alastair stepped down from Avacta in 2024. Avacta's valuation peaked in 2020 when its intraday market capitalisation approached US$1bn.

Advancing ambitions in targeted drug delivery technologies

The use of nucleic acids (RNA/DNA) as therapeutics instead of small molecules or biologics is an area of rapidly growing interest and commercial value. The RNA therapeutics market alone was valued at US$13.7bn in 2023 and projected to grow to US$18bn by 2028, according to forecaster MarketsandMarkets. Challenges associated with the manufacturing and targeted delivery of RNA therapeutics are a significant limiting factor, however, which N4 Pharma is addressing through its Nuvec® technology. N4P aims for it to become an industry leading platform used by multiple pharmaceutical partners, while also advancing its own drug pipeline.

RNA is typically a single-strand biopolymer that is vulnerable to hydrolysis. Being highly unstable, it requires a delivery system for use in the body as a therapeutic. Unlike other currently available delivery systems, which are based primarily on lipid nanoparticles or viruses, Nuvec® utilises silica nanoparticles that have a unique irregular (or 'spiky') surface structure, coated with polyethyleneimine ('PEI'), that effectively traps and protects the nucleic acid payload (siRNA/mRNA/DNA) as it travels to diseased cells.

Recent work indicates that Nuvec® has some significant benefits over other approaches. For example, it can be loaded with more than one RNA payload meaning that multiple therapies can be delivered to exactly the same cell where they can work simultaneously in combination. Protection of the

Stock Data

Share Price	0.68p
Market Capitalisation	£2.68m
Shares in issue:	394.78m
52 week high/low	1.50p/0.37p

Company Profile

Sector:	Pharmaceuticals
Ticker:	N4P
Exchange:	AIM

Activities

N4 Pharma plc ('N4 Pharma', 'N4P' or 'the Group') is a specialist pharmaceutical company nanoparticle and try developing a novel silica nanoparticle delivery system for vaccines and therapeutics for licensing to pharmaceutical and biotech partners.

www.n4pharma.com

5-year share price performance

Source: LSE

Past performance and forecasts are not a reliable indicator of future results.

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payload by the silica structure also means that delivery into a hostile environment (such as the gut) is possible permitting, for example, treatment of gastrointestinal disorders. Future development could potentially allow for systemic dosing via an oral capsule, thus avoiding repeated hospital visits for injections.

Reliable therapeutic targeting is clearly the holy grail for novel drug delivery systems and substantial, industry-wide resources are presently dedicated to this particular ambition. Such therapies introduce important benefits, ranging from low drug dosage, high efficacy, improved quality of life and fewer side effects; targeted nanocarriers can also result in improved bioavailability by utilising various drug mechanisms.

Considerable value is expected to be created in coming years, as a limited number of potentially successful targeting solutions emerge. N4P considers Nuvec® has the potential to be one of them. The required technology is being created through N4P's collaboration with Silicon Valley-based SRI International ('SRI'), which combines SRI's Fox Three Molecular Guidance System™ ('MGS') targeting peptide with Nuvec®. Early data suggests that the compounds generated do indeed result in targeted delivery of an RNA payload. Progressing this opportunity, N4P is also working on its own targeting mechanisms within its lead Nuvec® programme, N4 101, an anti-inflammatory treatment for inflammatory bowel disease ('IBD'). In addition to the significant benefits identified, Nuvec® also has the advantage of being straightforward to manufacture and load, while appearing to have no cytotoxicity issues/complications at the concentrations likely to be used.

By contrast, Avacta's pre|CISION® platform, which Dr Smith was responsible for identifying, acquiring and advancing into the clinic, masks toxic chemotherapy warheads by binding them to a short, engineered peptide that is cleavable only by the tumour-specific protease, fibroblast activation protein ('FAP'). The peptide is designed to disable the warhead before the cleavage step releases it to exclusively target the tumour microenvironment.

By focusing its currently limited resources on Nuvec®, N4P expects to deliver significant long term shareholder value through advancement of specific products in its pipeline that target diseases with defined, addressable markets. In the nearer term it will also be seeking to maximise opportunity, profile and cash generation through selected licensing of the platform to partners with non-competitive programmes.

One example (amongst several) of a similar technology platform that has successfully developed its own products and secured a multi-target collaboration with GSK (announced in December 2022), is Wave Life Sciences, Inc. (NASDAQ: WVE). Encompassing three clinical programs focussed on siRNA and RNA editing, this high-value deal brought together WVE's PRISM™ oligonucleotide platform and GSK's expertise in genetics and genomics. It comprised an upfront payment of US$170m and potential milestones totalling of up to US$3.2bn.

Funding sufficient to support work programmes out to end-H1 2025

N4P is a highly efficient, virtual biotech company. Its principal focus is on the advancement of its lead Nuvec® programme, N4 101 and building-out a comprehensive data set to demonstrate the key benefits of the platform as described above in order to support commercial activities and partnering in the nearer term.

Despite this ongoing workload, FY2023's operational burn of c.£0.1m/month (net of R&D tax credit) is thought to have increased only marginally during FY2024. The Group successfully raised £0.63m (gross) new funding through an equity placing and subscription ('the Placing') on 7 June 2024. Together with a cash balance of c.£0.5m held at that time, N4P is thought to have sufficient resources to support planned operations through to around mid-2025.

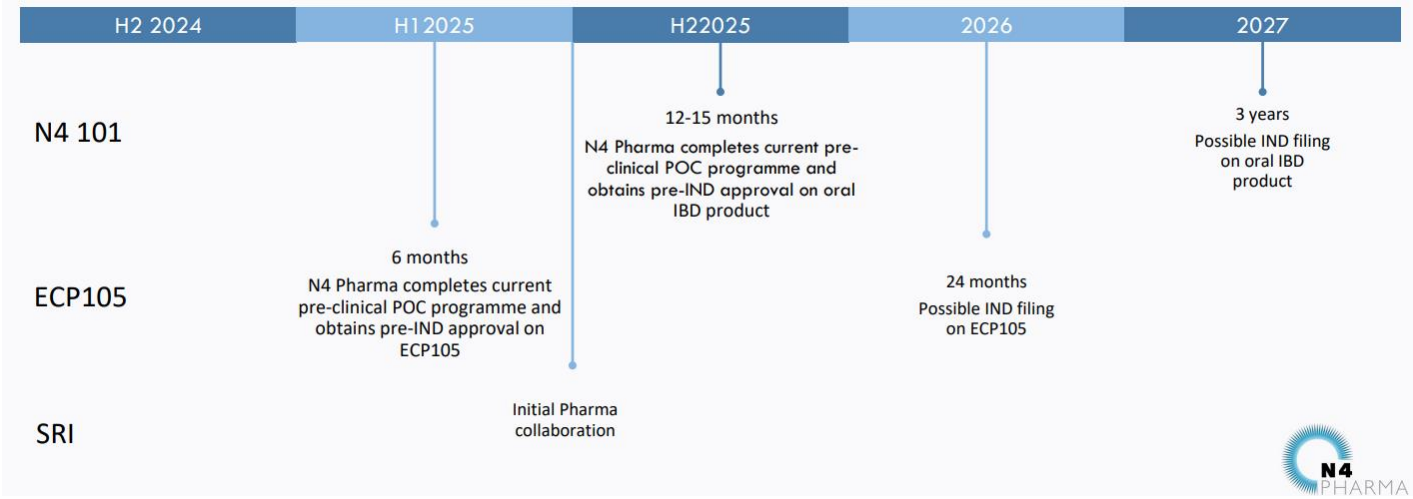
N4 Pharma's targeted news flow

N4P's two novel and complementary, patent protected non-viral delivery technologies are expected to deliver significant advances over the coming 18 or so months. This is expected to further raise their profile which, against a background of significant demand in the gene therapy space for targeted gene delivery, opens various opportunities to commence potentially lucrative third-party licensing negotiations particularly for Nuvec® which appears to solve several of the key challenges the sector is facing right now. A comprehensive and compelling data

set is key to securing meaningful licensing deals. Building this data set, which can be done at relatively modest cost, and which will also complete some of the necessary steps in developing N4 101 towards an IND filing and clinical trials, is the near-term focus. It is designed to attract game changing commercial partnerships while at the same time advancing N4 101 to the clinic. Research at Nanogenics for ECP105, and collaborative work with SRI on targeted therapeutic delivery will continue; both have the potential to deliver significant news flow.

Based on projected expenditure, N4P expects to reach (amongst other things) a number of key valuation inflexion points over the coming years. Each of these are expected to progress it toward prospective licensing (or even trade sale) opportunities. Three important releases being targeted for the current financial year are detailed below:

N4 Pharma - Anticipated Value Inflection Points in Coming Years



Source: N4 Pharma, Investor Presentation October 2024

N4 101 – Orally delivery RNA treatment for IBD to replace regular injections

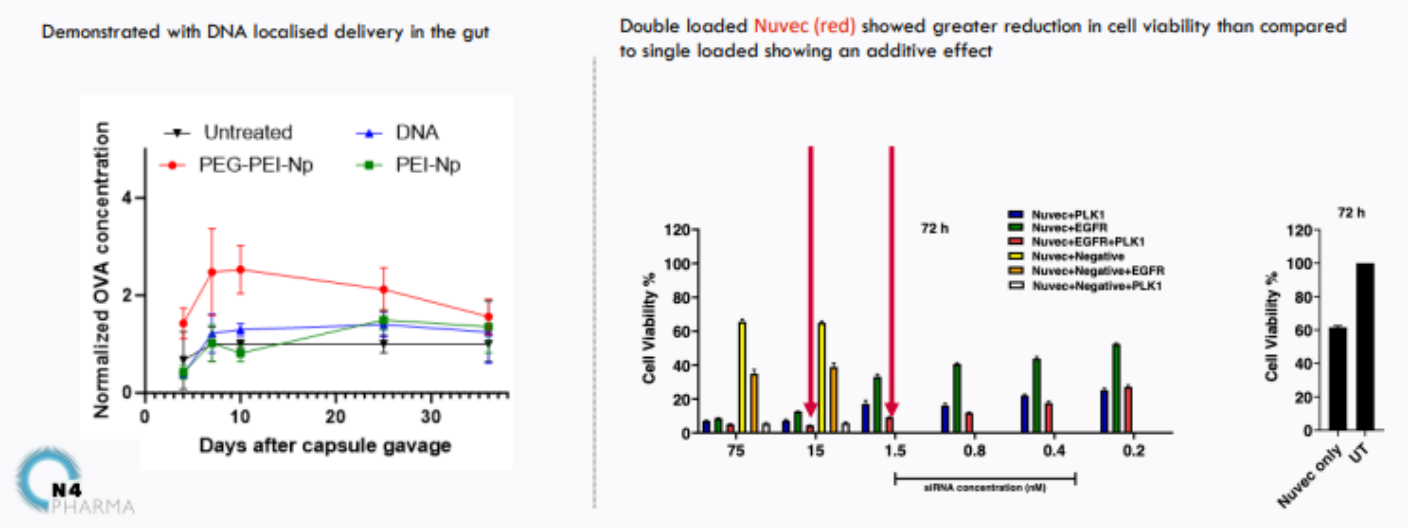
N4 101 is an orally delivered inflammation inhibitor for IBD, designed to showcase the key benefits of the Nuvec® delivery technology. The capsule contains Nuvec® dual loaded with two RNA sequences, one to reduce production of a protein associated with inflammation and the other to promote the body's own anti-inflammatory response, for local delivery to the GI tract. N4 101 also has an additional targeting element chemically added to the Nuvec® particle's surface which is aimed at specifically targeting macrophages responsible for the inflammation.

Recent *in vitro* experiments used mouse-extracted cells to establish the ability of Nuvec® delivered its RNA cargoes to (i) Reduce the production of TNF-alpha which is a chemical produced by the immune systems that causes inflammation and, (ii) Increase the expression of IL-10 (a molecule that has an anti-inflammatory role). In the treatment of an inflammatory condition (such as IBD) a reduction in TNF-alpha production and an increase in IL-10 is desirable.

A patent has already been filed in order to protect the clear advantages Nuvec® introduces for targeting and dual loading. N4P also presently awaits ethics committee approval to build on the strong *in vitro* data prior to commencing *in vivo* studies in an appropriate animal model at the University of Queensland early in 2025.

Current therapies for IBD which target TNF-alpha inhibition are effective but come with numerous issues, including tolerability, non-response and immune sensitivity. Antibody therapeutics, known as TNF-alpha inhibitors, presently offer the best treatment and represented c.78% of the market in 2022 even if regular, inconvenient injections somewhat reduce patient compliance. As a result, the trend is shifting toward preferred oral treatment in the form of Janus Kinase inhibitors ('JAKs'), even though the product's lack of tissue selectivity can result in toxicity issues in other organs.

N4 Pharma - N4 101 Current Progress



Source: N4 Pharma, Investor Presentation October 2024

The global market for IBD, comprising over 8m suffers and split principally into two different conditions (Crohn's disease and ulcerative colitis), was valued at US$20.4bn in 2023 and is projected to expand by a CAGR of 3.9% to over US$27.6bn by 2030 according to a report published by Grand View Research. Oral administration can provide a cost-effective method to deliver nucleic acid therapies with improved levels of patient compliance. In H2 2025, N4P expects to seek pre-IND approval for N4 101, which it will position as a prospective replacement for JAKs and opening a market opportunity that was valued at c.US$7bn/year in the same research note.

N4 101 therefore represents an efficient use of shareholder capital to both advance a commercially valuable and proprietary product to the point of commercialisation (or joint venturing), as well as providing a vehicle to continue to build out the detailed data package required to secure meaningful partnering deals on a shorter timescale.

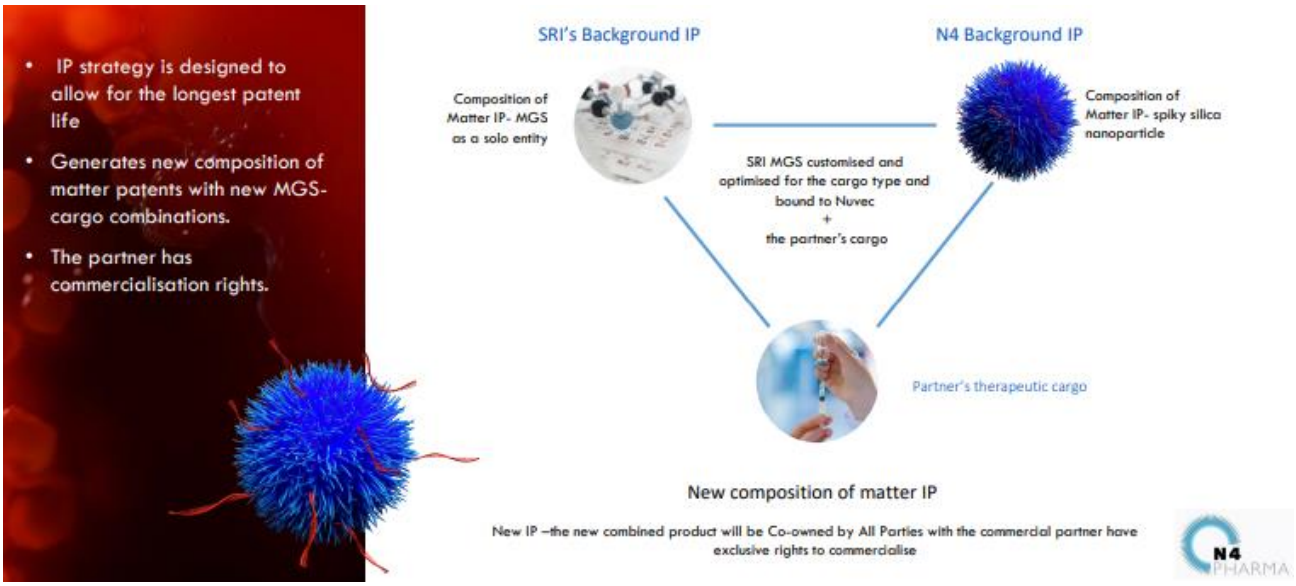
SRI International collaboration to commence third-party marketing around mid-2025

First established in April 2024, this collaboration seeks to develop an improved delivery platform for nucleotide therapies by combining the key advantages of N4P's Nuvec® nanoparticle (including protection of nucleic acid cargos from enzymatic breakdown and its ability to carry high/complex payloads), with improved cellular targeting through utilisation of SRI's Fox 3 Molecular Guidance System™ targeting peptide ('MGS'). The first stage of this collaboration demonstrated that a particle (or compound) created by the combination of the two technologies can be directed and exclusively taken-up into target cells whereupon it delivers the desired biological effects, i.e., knockdown (or reduction) of the production of a specific protein.

The ability to target different tissue types represents a key differentiator to competing nucleic acid delivery approaches, such as that presently offers through the N-acetylgalactosamine ('GalNAc') platform, or the more advance lipid nanoparticles/viral particles. Although it is widely used in gene silencing therapies to deliver siRNA, GaINac can only target hepatocytes (primary cells in the liver), while modifying lipid or viral particles in order to target specific tissues is far from straightforward or routine at the present time.

With over 50 MGSs available, SRI is able to target a variety of cell types and can deliver an array of molecules, including nucleic acids, proteins and nanoparticles. Supporting data is now being collected from a range of additional MGS combinations for assessment. Subject to a satisfactory outcome, initial presentations to major pharma players to propose joint development projects and/or licensing are expected to commence.

SRI/N4 Pharma Intellectual Property Strategy



Source: N4 Pharma, Investor Presentation October 2024

ECP105 - Targetting an unmet clinical need in the ophthalmology market

Early in 2024, N4P acquired a controlling interest, through a subscription for new ordinary shares, in Nanogenics Limited, a company with a complementary lipid and peptide-based delivery system called LipTide®, which it is presently using to develop a novel siRNA product that targets an unmet clinical need in the ophthalmology market.

Failure rates post-glaucoma surgery due to fibrosis can be as high as 50% over the subsequent 5 years. Current treatments to prevent fibrosis (e.g., mitomycin C ('MMC')) are unlicensed and introduce severe risk of side effects. ECP105, which consists of a siRNA sequence that silences MRTFB, a gene implicated in the promotion of fibrosis, has been encapsulated by the LipTide® delivery system to address this unmet need. In so doing, it provides a simple and effective anti-fibrotic therapy to maximise surgical success in glaucoma by reducing post-surgical scarring without exposing patients to the risk of cytotoxic medication.

Glaucoma, a chronic, progressive eye disease characterised by damage to the optic nerve, currently affects 80 million people worldwide. Driven by population aging, this has been projected to rise to nearly 112 million by 2040. It is estimated that 300,000 Glaucoma Filtration Surgeries (trabeculectomy) presently take place worldwide annually; other procedures similarly lead to scarring. Treatments are said to typically cost around US$6,500 per surgery, compared with application of EPC105 that is expected to be in the range of just US$600 to US$1,000. Replacing the use of off-label MMC, this implies a market size of US$180m to US$300m per annum with opportunity for repeats should there be a need for further surgery.

A pilot *in vivo* study conducted by London's King's College that demonstrated ECP105 to have activity comparable to microfluidic formulation. Delivered to the eye by a single subconjunctival injection (LipTide® with 25ug MRTF siRNA) in a rabbit model, treatment led to a doubling in bleb survival and matching the current gold-standard MMC treatment. Crucially, no adverse side effects were observed. A full *in vivo* study is expected to begin later this year. Meanwhile, formulation work is ongoing in anticipation of the Group scoping out a regulatory planning dossier to take ECP105 through to a pre-IND meeting with the FDA. The outcome of this meeting should guide the timing, design of any follow-on *in vivo* work and subsequent preparation for design of the initial IND study (expected mid-2026).

N4P also awaits the result of its application for orphan drug designation status for ECP105 which, if granted, would give seven years exclusivity in the USA on the product post authorisation, along with potential tax credits, eligibility for grants and an accelerated approval process.

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