Stock Data

Share Price	0.775p
Market Capitalisation	£2.08m
Shares in issue:	268.78m
52 week high/low	2.70p/0.71p

Company Profile

Sector:	Pharmaceuticals
Ticker:	N4P
Exchange:	AIM

Activities

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

www.n4pharma.com/two

5-year share price performance

Source: LSE

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

Turner Pope contact details

Tel: 0203 657 0050
Email: info@turnerpope.com
Web: www.turnerpope.com

Andrew Thacker
Corporate Broking & Sales

Barry Gibb
Research Analyst

Turner Pope acts as joint broker to N4 Pharma plc.

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N4 Pharma plc

N4 Pharma has released an update on its ongoing *in vitro* double-loaded siRNA research work. It is investigating the ability of Nuvec® nanoparticles to be loaded with and concurrently deliver, two different siRNA known to inhibit relevant oncology targets. Through application of multiple different constructs, it has demonstrated that such loading can be undertaken without changing the size or charge of Nuvec®, which are two essential parameters for successful cellular uptake. While the *in vitro* findings did highlight the complex nature of multiple pathway targeting, including an apparent reduction in knockdown of EGFR (epidermal growth factor receptor), it is significant that reduction in cell viability was always retained. As such, Nuvec® is demonstrating a highly innovative and much needed approach to more effective cancer treatments by reducing the ability for tumour escape. Retaining a cash runway that extends into H2 2024 and with additional work exploring siRNA concentrations and dose loading now underway, which may be followed by further *in vivo* studies, as well as the possibility for other updates covering N4P's ongoing oral and AAV viral vector work, the coming months look to be particularly news heavy. In this respect, the intense focus on RNA therapy that followed the success of COVID vaccines suggests further preclinical and clinical validation could open up third party partnering/licencing opportunities for both this and/or the Group's LipTide® platform, which was secured through the recent Nanogenics Limited acquisition.

Cutting edge nanoparticle delivery system research

The use of nanoparticles as a delivery system is a relatively new concept and so demands quite exhaustive assessment across multiple constructs in order to comprehensively understand the cellular process involved. Recent months have seen N4P investigating the ability of Nuvec® nanoparticles to be loaded with and concurrently deliver two different siRNA known to inhibit relevant oncology targets. Significantly, this has been undertaken without changing the size or charge of the delivery system, one of the essential parameters for successful cellular uptake.

Initial work on cell growth involved investigating the combination of inhibition of EGFR and BCL-2: (B-cell lymphoma 2) using PC-9 cancer cells. As detailed previously, when separately loaded onto Nuvec®, each siRNA achieved cell inhibition and an assay to measure BCL-2 was established. Subsequent work has confirmed that the expression level of BCL-2 in PC9 cells was at the limits of detection, and consequently (unlike with EGFR), a knockdown response curve could not be measured.

Given such low expression, alternative cellular pathways that may be inhibited using siRNA loaded alongside EGFR have now also been investigated. The first was BRD4 (Bromodomain-containing-protein 4) a target for which inhibitors are currently being evaluated in clinical trials in uveal melanoma, leukaemia and carcinoma. The second was PLK1 (Polo Like Kinase 1), being target inhibitors that are in early clinical trials for lymphoma and pancreatic cancer. N4P may explore additional targets as its work progresses.

Testing the effect of both BRD4 and PLK1 upon combination with EGFR, individually they demonstrated the expected outcome of a dose dependent inhibition of cell growth and target knockdown but, somewhat surprisingly, when loaded together there was an interaction which resulted in a reduction in knockdown of EGFR receptor. Most significantly, however, reduction in cell viability was retained.

Such *in vitro* findings highlight the complex nature of multiple pathway targeting. Further investigative steps are already underway to establish the mechanism responsible for the interaction between two separate siRNA on target knockdown when loaded on Nuvec®. One suggestion is that there is not a direct correlation between the degree of knockdown and the functional effect on cell death. Varying the amount of each siRNA loaded onto the delivery system, to see how these change the degree of interaction whilst maintaining cellular inhibition is one way to prove such a theory, while in tandem assessing minimum dose required to achieve the same endpoint. Dose sparing, of course, could demonstrate a further important advantage when using Nuvec®. Beyond this, N4P is expected to consider further *in vivo* studies and their scope as this work concludes whilst, in parallel, supplying potential collaborators with *in vitro* data as it is gathered.

Championing a novel approaches to treatment of cancer

N4P's novel approach to cancer treatment does not rely on the immune response, nor incur the general toxicity induced by chemotherapy or radiotherapy. Instead, it targets well-known growth factor pathways spurring tumour growth that are key to addressing the shortfalls of immunotherapeutic and chemotherapeutic approaches. It also recognises that although some monoclonal antibody treatments ('mAbs') do target tumour growth dependent pathways, they have highly significant off-target effects, must be given repetitively, can be immunogenic, and address only one pathway at a time. This allows for the emergence of tumour populations that proliferate by other growth pathways, meaning that none have been curative.

The Group instead seeks to utilise multiple siRNAs capable of simultaneously targeting identified pathways responsible for cancer progression after initial treatments. Knocking down both (or more) pathways offers a greater chance that tumours will not develop resistance or otherwise proliferate through the emergence of an alternative growth pathway(s), which has been seen to be a common outcome in existing treatments that block a single growth factor pathway.

N4P Finances - Runway sufficient to take it to the start of H2 2024

TPI estimates that N4P's recent acquisition of Nanogenics Limited will have lifted the Group's cash burn from a little over £100k/month during H1 2023 to around £130k/month from Q4 2023 and going forward into the new financial year. With c.£1.29m cash/cash equivalents in the Group's balance sheet at end-June 2023, there appears to be runway sufficient to take it to the start of H2 2024 based on current programmes/schedules, although any decision to further ramp up of development of either of its delivery platforms or its new key preclinical candidate will likely bring this schedule closer.

Commercialisation Strategy - Focusing on strong commercial point of difference

Having already refined its near-term commercial strategy in order to highlight Nuvec®'s specific point of difference as a carrier of multiple siRNA compounds, the majority acquisition of Nanogenics now introduces a highly complementary but differentiated non-viral delivery technology along with a lead candidate that appears capable of securing a relatively quick route to clinic. Importantly, this opens opportunities to identify technical synergies through parallel development programmes involving both delivery platforms, while preclinical and clinical validation could open up third party licencing opportunities either individually or for both.

This is particularly exciting given that Nuvec® has already demonstrated ability to deliver multiple siRNA into the same cell, therein providing a unique solution for combination therapy treatments. Given that many drug development companies are presently undertaking early-phase preclinical/clinical testing/trials, they are

generally more open to new, novel solutions than those at more advanced stages. Following its signing of two Material Transfer Agreements ('MTAs') back in 2021, one of which was a with major company in gene therapy and the second with a company developing its own DNA Covid vaccine, this work continues while the Group seeks further such partnership opportunities and, as such, the pace of progress here is largely determined by N4P's partner's own R&D work and drug launches.

Based on feedback from the patent examiner and further work the Group has already completed, it has been demonstrated that combining Nuvec® with adenoviral vectors (in addition to its earlier work on lentiviral vectors) can lead to an improvement in vector performance and a reduction in the amount of the viral vector required. Accordingly, it is presently pursuing patent applications in Europe (including UK); USA; Japan; India and Canada (and intends to file similar applications in Australia and China in due course) which, if granted, would be in addition to those already exclusively licensed from the University of Queensland ('UQ') in an effort to further strengthen the commercial protection of the delivery system. N4P is also exploring next generation use for oral delivery plus potential improvement in the application of viral vectors. Positive preliminary results from ongoing studies undertaken at UQ demonstrate orally delivered Nuvec® is capable of transfecting cells in the small intestine. The next step in this work is for UQ to repeat the success of this through an *in vivo* study, which management understands will be undertaken shortly.

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