N4 Pharma plc

This week and last, N4 Pharma released positive siRNA updates. Having successfully undertaken single loading of both the EGFR and BCL-2 siRNA nucleotides onto Nuvec®, which produced good monodisperse formulations, single loaded EGFR siRNA demonstrated strong silencing of the EGFR gene with a dose response curve established. Overcoming some temporary siRNA supply issues, the Group has subsequently also completed work on establishing assays to measure how Nuvec® loaded with BCL-2 siRNA can silence expression of the BCL-2 protein. Significantly in this respect, *in vitro* studies indicate inhibition profile similar to two commercial therapies, namely Gefitinib (for EGFR) and Venetoclax (for BCL-2). Follow on work is now being planned to assess the lowest siRNA loading on Nuvec® to achieve comparable cellular apoptosis to these drugs, while also constructing a full *in vitro* dose response curve study to permit comprehensive assessment by interested parties. Generation of such data along with results from *in vivo* studies that are due to get underway shortly, should represent a further important step toward delivering the proof of concept ('PoC') required to attract large pharma and biotech partners into collaborations to explore Nuvec® as their chosen delivery system to get products into clinic and potentially speed its route toward commercialisation. Having completed an equity Placing and Broker Offer on 22 November 2022 that raised £1.05m (gross), N4P's net cash at end-December 2022 stood at £1.9m. Based on TPI's assumption that cash burn rises from last year's sub-£100k/month to c.£135k/month for the whole of 2023, the Group presently has sufficient runway to complete its proposed testing programme along with scheduled marketing outreach exercises and further development work on oral delivery/viral vector improvement etc., over the coming 12 or so months.

Successful development work on multiple loaded siRNA

On 14 September 2022, N4P provided an operational update on its development plans for commercialising Nuvec®, the Group's unique silica nanoparticle delivery system for reformulations and development of cancer treatments and vaccines. Having uncovered a unique ability to concurrently load multiple siRNA compounds onto Nuvec®, enabling both to be concurrently taken up into the same cell, initial testing was undertaken using two generic siRNA probes, GFP ('Green Fluorescent protein') and EHMT-2 ('Euchromatic Histone Lysine Methyltransferase 2').

Following successful completion of this work, the Board undertook a strategic review to consider where it was likely to achieve the greatest and most rapid commercial traction. Given Nuvec®'s preclinical status, it concluded that development efforts should focus on loading more than one siRNA sequence onto the same nanoparticle. The ambition here being to silence complimentary pathways, in turn leading to an increased therapeutic response while establishing a significant differential in this marketplace.

Accordingly, the next step was to test *in vitro* whether Nuvec® loaded with both forms of siRNA is able to silence both targets. By 4 October 2022 this work had been completed. Allocated in equal amounts at a concentration previously shown to be active, testing demonstrated that both were able to

Stock Data

Share Price	2.20p
Market Capitalisation	£5.14m
Shares in issue:	233.78m
52 week high/low	3.98p/1.50p

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/

5-year share price performance

Source: LSE

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

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significantly silence their respective targets. This provided sufficient validation for N4P to begin the further testing, starting with *in vitro* EGFR (epidermal growth factor receptor) and BCL-2 (B-cell lymphoma 2) studies in a PC9 lung cancer model. EGFR, for example, is found on the surface of some normal cells and is involved in cell growth, but high levels have also been identified on some types of cancer cells and is responsible for their rapid expansion.

N4P's announcement of 1 April 2023 confirmed that the single loaded EGFR siRNA demonstrated strong silencing of the receptor's gene with a good dose response curve established. By 25 April 2023, temporary siRNA supply issues that had delayed establishment of the BCL-2 assay to be used had been overcome, and the Group is now proceeding to generate a similar dose response curve for knockdown of BCL-2 expression. Once this work is complete, having already established the growth curve of the xenograft tumour model to be used, N4P will be ready to commence *in vivo* studies (assuming there are no further siRNA supply issues).

In vitro studies indicate similar inhibition profile to two commercial therapies

In vitro studies have demonstrated that the maximum inhibition of cell growth by siRNA to either EGFR or BCL-2 loaded on Nuvec® was comparable to that produced by two commercially available small molecule drugs, Gefitinib (for EGFR) and Venetoclax (for BCL-2).

Gefitinib: Sold in Europe and Asia, this targeted small molecule cancer drug operates as a tyrosine kinase inhibitor ('TKI'). Tyrosine kinases are proteins that send signals instructing cancer cells to grow and divide; utilising their receptors for EGFR, Gefitinib blocks these signals to limit tumour proliferation.

Venetoclax: Under the brand names of Venclexta and Venclyxto, this type of targeted therapy drug is called a BCL-2 inhibitor (blocker). It is used to treat adults with chronic lymphocytic leukaemia, small lymphocytic lymphoma, or acute myeloid leukaemia, whose diseased cells are seen to produce excessive amounts of the BCL-2 protein.

Further work is now planned to assess the minimal loading of siRNA on Nuvec® to achieve comparable inhibition to these two approved drugs. The next step in the *in vitro* research work is to undertake a full dose response curve study for siRNA loaded Nuvec® and compare this to similar published data for Gefitinib and Venetoclax.

Successful completion could provide strong clinical validation for using Nuvec®

Because N4P cannot take relevant generic vaccines into the clinic itself without significantly increased expenditure, the Board decided to focus its development work on oncology and siRNA delivery as these sectors have proven clinical models it can access. Furthermore, Nuvec® can be used to work with generic siRNA and plasmids capable of being incorporated in phase 1 clinical trials, which are increasingly found in development as therapeutics, particularly in oncology and gene therapy.

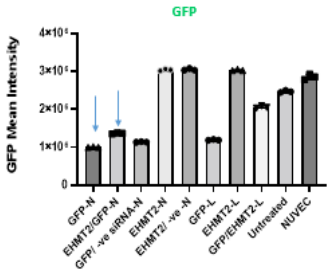
At present, delivery of multiple siRNAs would require multiple carriers, thereby decreasing the probability of transfecting the same cell with more than one siRNA, while hitting multiple aspects of a cellular pathway is also less likely. Delivery of two siRNA acting on two complimentary pathways in the same cell, therefore has the potential to provide an improved clinical response with lower adverse events compared to conventional chemotherapy.

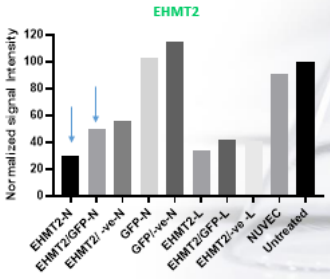
There are said to be over 300 companies presently working in this space, with 106 clinical trials already in place using siRNA. The Group's strategic focus therefore provides two clear advantages in that: (i) It is able to identify a wider target audience and; (ii) The number of compounds it can use to collaborate with provide the opportunity to get into the clinic much more rapidly than if it were to concentrate purely on vaccines.

Results of Initial *in vitro* Testing of Nuvec® Loaded with Two Generic siRNA Probes

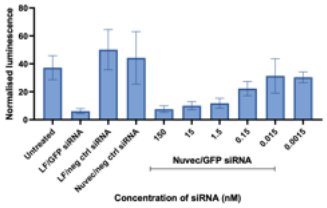
Silencing both GFP and EHMT with 2x loaded Nuvec

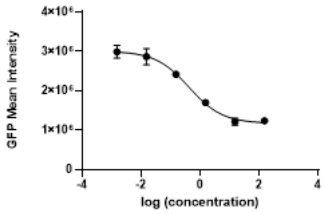
- Nuvec loaded with both GFP and EHMT2 siRNA 50/50 mix
- Double loaded particles were then tested on both targets
- Both targets significantly knocked down





Silencing GFP with siRNA loaded onto Nuvec

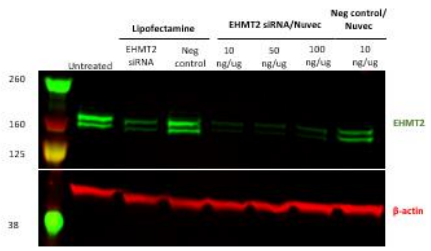


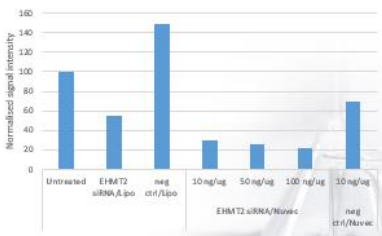


IC_{50}: 0.415 nM of siRNA (with 70 ug/ml of Nuvec)

- Cells carrying the GFP gene were transfected with Nuvec loaded with silencing siRNA and compared to
  - Untreated
  - GFP siRNA/lipofectamine
  - Non relevant siRNA/lipofectamine (neg) or Nuvec (neg)
- The cells transfected with siRNA GFP loaded onto Nuvec showed strongest silencing effects on the cells
- **A clear dose response was seen that was comparable and even outperformed lipofectamine transfection with GFP siRNA**

Silencing EHMT2 with siRNA loaded onto Nuvec





`Source: N4 Pharma, Investor Presentation, October 2022

Commercialisation Strategy - Focusing on strong commercial point of difference

N4P has refined its immediate commercial strategy to focus on and highlight Nuvec®'s specific point of difference as a carrier of multiple siRNA compounds that has been uncovered by its research and development. The ability to deliver multiple siRNA into the same cell provides a unique solution for combination therapy treatments. Given that many drug development companies are presently undertaking early-phase pre-clinical/clinical testing/trials, they are generally more open to new, novel solutions than those at more advanced stages.

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 shortly undertaken.

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