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**N4 Pharma plc**
**("N4 Pharma" or the "Company")**

**Nuvec® R&D and Strategy Update**

N4 Pharma Plc (AIM: N4P), the specialist pharmaceutical company developing Nuvec®, a novel delivery system for cancer treatments and vaccines, is pleased to provide an encouraging update on its ongoing *in vitro* siRNA research work.

The Company's double loaded siRNA work is ongoing and the Board wishes to provide an update on the progress achieved so far, as we reach the end of 2023. The work to date is very encouraging and is demonstrating that Nuvec® has considerable potential to be able to knockdown two independent pathways leading to more effective cancer treatments by reducing the ability for tumour escape.

***Nuvec® R&D***

For the past few months, the Company has been investigating the ability of Nuvec® nanoparticles to be loaded with, and deliver at the same time, two different siRNA known to inhibit relevant oncology targets. This is cutting edge research in the use of nanoparticles as delivery systems in oncology and consequently the Company is proceeding carefully to ensure that it gains the maximum understanding of the cellular processes involved.

Using multiple different siRNA constructs has demonstrated that two separate siRNA can be loaded onto Nuvec® without changing the size or charge of Nuvec®, both parameters being essential for successful cellular uptake.

The initial work on cell growth involved investigating the combination of inhibition of EGFR (epidermal growth factor receptor) and BCL-2: (B-cell lymphoma 2) using PC-9 cancer cells. As previously announced, each siRNA when separately loaded onto Nuvec® achieved cell inhibition and an assay to measure BCL-2 had been 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.

In view of the low BCL-2 expression, the Company has been investigating alternative cellular pathways that may be inhibited using siRNA loaded alongside EGFR. The first was BRD4 (Bromodomain-containing-protein 4) a target for which inhibitors are currently being evaluated in clinical trials in uveal melanoma, leukemia and carcinoma. The second target was PLK1 (Polo Like Kinase 1), inhibitors of which are in early clinical trials for lymphoma and pancreatic cancer. Additional targets may also be explored as the Company's work progresses.

As with the other siRNAs explored to date, Nuvec® can be loaded with the individual SiRNA and effect knockdown of the respective targets and reduce cell viability in a dose related manner.

Having confirmed dual loading of Nuvec®, the Company subsequently tested the effect of BRD4 combined with EGFR and PLK1 combined with EGFR on knockdown and cell viability. Although individually both siRNA had demonstrated the expected results of a dose dependent inhibition of cell growth and target knockdown, when loaded together there was an interaction which resulted in a reduction in knockdown of EGFR receptor but importantly the reduction on cell viability was retained.

The mechanism responsible for the interaction between two separate siRNA on target knockdown, when loaded on Nuvec® is under investigation. One explanation is that there is not a correlation between the degree of knockdown and the functional effect on cell death. In particular, the Company is exploring varying the amount of each siRNA loaded on Nuvec® to see how these change the degree of interaction whilst also maintaining cellular inhibition. Investigations will also be undertaken to see how low the dose can be reduced to still achieve a functional cell inhibition endpoint as dose sparing could be another useful advantage when using Nuvec®.

***Oncology Strategy***

It is likely that the precise combinations of siRNA, both in terms of target and concentration of siRNA, will vary depending in which cell type they are tested in. Both these elements will be determined by the clinical outcome desired.

Chemotherapy treatments for cancers are broad stroked and have very high toxicity which has led to the emergence of alternative immuno-oncology treatments. These have had remarkable success for some cancers but have proved ineffective in curbing the progression of numerous cancers. Single pathway treatments can have an initial effect but many see the post treatment emergence of cancer cells that have developed "immune escape" pathways leaving retreatment as futile.

Novel approaches to treatment of cancer that do not rely on the immune response, nor incur the general toxicity induced by chemotherapy or radiotherapy, but rather rely on targeting the well-known growth factor pathways spurring tumour growth are key to addressing the shortfalls of immunotherapeutic and chemotherapeutic approaches. 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 target only one pathway at a time, allowing for emergence of tumour populations that proliferate by other growth pathways. None have been curative.

The work the Company is doing shows that Nuvec® can bind not only single, but multiple siRNAs aimed at simultaneously targeting identified pathways responsible for cancer progression after initial treatments. Knocking down both (or more) pathways will give a greater chance that tumours will not develop resistance, escape and again proliferate by the emergence of a significant alternative growth pathway, which is common in treatments blocking just one growth factor pathway.

The *in vitro* findings are highlighting the complex nature of multiple pathway targeting and the Company we will look at 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.

The Company's oral and AAV viral vector work is also ongoing and further updates will be provided in due course, along with news regarding the recent acquisition of a controlling interest in Nanogenics Limited.

**Nigel Theobald, Chief Executive Officer of the Company, commented:**

*"There has been a lot of work undertaken in what is a highly complex scientific area and we have repeatedly shown that Nuvec® is successful in always loading and delivering dual siRNA, however the interactions between the siRNA vary depending on which two are chosen and which cells they are tested in so we continue to test these interactions.*

*"The work we have done so far is extremely encouraging and is demonstrating that Nuvec® has considerable potential to be able to knockdown two independent pathways leading to more effective cancer treatments by reducing the ability for tumour escape. This is a highly desirous and innovate approach in developing novel cancer treatments*."

**For more information please contact:**


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**About N4 Pharma**

N4 Pharma is a specialist pharmaceutical company developing a novel delivery system for oncology, gene therapy and vaccines using its unique silica nanoparticle delivery system called Nuvec®.

N4 Pharma's business model is to partner with companies developing novel antigens in these fields to use Nuvec® as the delivery vehicle for these antigens. As these products progress through pre clinical and clinical programs, N4 Pharma will seek to receive upfront payments, milestone payments and ultimately royalty payments once products reach the market.

For further information on the Company visit www.n4pharma.com or sign up at www.investors.n4pharma.com.

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