RNS Number : 0367S
N4 Pharma PLC
06 July 2020

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

Work Programme and Strategic 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 update on its optimisation programme, proof of concept work on Covid-19 and a new initiative to explore Nuvec®'s potential as an oral delivery system.

Optimisation Programme

Work has continued on the Company's optimisation programme during the Covid-19 pandemic and resulting lock down. That said, contrary to initial expectations, progress has been slower than originally hoped as the rota system employed by the main laboratories contracted for this work has seen the optimisation of the DNA loading take longer than expected and this work remains ongoing. However, these delays have been supplemented by the proof of concept work utilising Nuvec® being undertaken by Evotec International Gmbh ("Evotec") as detailed below.

In respect of the Company's collaboration work with Nanomerics at UCL School of Pharmacy, N4 Pharma is pleased to announce that with effect from 13 July 2020, Nanomerics will be able to undertake a gradual return to the laboratories to continue its work under the research collaboration agreement announced on 11 February 2020. Prior to suspension of activities due to the lockdown, Nanomerics had demonstrated that polyethylenimine ("PEI") loaded Nuvec® could be dispersed and resuspended in an aqueous solution ready for the loading of DNA. Assessment of the DNA loading characteristics will be the starting point when work resumes.

Covid-19 Studies

With respect to studies involving Covid-19, Evotec remains on track with the *in vitro* testing of Nuvec® loaded with the Covid-19 plasmid and, in conjunction with the Company, continues to look at ways in which it can accelerate the commencement of Stage 3 of the Covid-19 work (as set out in the Company's announcement on 16 April 2020) and perform the *in vivo* protein expression testing in parallel with the *in vitro* studies. Assays to detect the spike protein antigen arising from the plasmid transfection and the antibodies produced *in vivo* have been established by Evotec.

Strategic Update - Potential Oral Applications

The more work undertaken and data that has been collected on Nuvec®, the more the Directors have gained an understanding of the potential applications for Nuvec® which

could give it a competitive advantage over existing delivery systems that are currently in use. To date, the majority of work to explore Nuvec®'s potential has been centred on administering it by injection, in keeping with the vast majority of vaccines (both existing and in development) which use a parenteral administration of a dosage through injection; be it intravenous, subcutaneous or intramuscular. However, recent research on Nuvec® indicates that its unique spiky structure could give it a significant competitive advantage as a potential delivery system for use in oral vaccines.

Oral vaccine delivery offers a number of potentially significant advantages over other routes of administration, such as:

- oral vaccines are cheaper to administer, since they can be delivered outside of a formal clinical setting without the need for trained personnel;
- the elimination of needles from the vaccination process can minimize patient and caregiver trauma;
- it negates concerns regarding the reuse and disposal of needles, which has been shown to be responsible for a number of vaccination-related infections;
- oral vaccines may also be cheaper to produce, due to less stringent regulatory requirements for preparations that are administered orally compared with parenterally e.g. the reduced need for sterile manufacture; and
- as an enteric capsule lyophilised final product, storage conditions are less onerous than injectable products.

Notwithstanding all these potential commercial benefits, taken together, these advantages could make an oral vaccine particularly valuable to less developed countries where vaccinations can be particularly important in the protection of life of the most vulnerable.

Despite these potential advantages, there are a number of issues that need to be addressed to establish an orally delivered vaccine, and existing delivery systems used in the parenteral space are not well placed for this. In each case the data the Company has accumulated suggests that Nuvec® could be a viable solution to address these issues.

1. For effective oral immunisation, vaccine antigens (protein or DNA/RNA) must be protected from the acidic environment of the stomach and also protected from the proteolytic milieu of both the stomach and intestine. Lipid nanoparticles ("LNP") are not suited to lyophilisation but rather must be retained as a liquid or semi-solid formulation.

   Protection from the stomach acid and pepsin proteolysis can be achieved readily by delivering the product in acid resistant tablets or capsules. This is a well-established principle in pharmaceutical development and would be readily applicable to Nuvec® which has been shown to be suitable for lyophilisation. The monodisperse nanoparticulate product would be suitable for inclusion in an acid resistant capsule.

2. There are multiple types of lipid nanoparticles and some may be disrupted in the small intestinal fluid exposing the payload to digestion before it can be presented to the absorptive cells. Lipases may trigger lipid digestion and disruption of the LNP, while proteases/nucleases will initiate protein/DNA digestion.

   In general, a preformed silica nanoparticle will be more resistant to the digestive actions of the intestinal milieu. Previous studies have demonstrated that Nuvec®

reduced the digestive effect of nuclease enzymes on DNA/RNA when added to the incubation medium.

3. The other important feature of the gastrointestinal tract is the mixing and propulsive movement of contents in an oral-anal direction. Solid, undissolved matter will traverse the gut and be expelled without delivering the payload.

   Mucoadhesive properties of Nuvec®, resulting from the engineered design of long silica spikes coated with a cationic charge provided by PEI, will encourage binding to the mucosa cells.

Whilst there will be multiple other challenges to be addressed, the Directors feel that Nuvec®'s properties has the potential to position it as a superior delivery technology for oral vaccines. Furthermore, whilst agglomeration has presented itself in certain parenteral studies with Nuvec®, and this is being addressed through the optimisation work, it may be less of a concern in oral administration. In exploring the potential for Nuvec®'s use for oral delivery, the Company's focus will be on addressing the issues identified above to increase the viability of oral administration of vaccines, in order to benefit from the vast commercial prospects and advantages identified above.

Notwithstanding the indicative evidence that Nuvec® could work orally, there are a number of steps to be taken to progress this potential. To that end the Company will working with Evotec to undertake some preliminary *in vitro* studies to establish first that Nuvec® can be optimised to transfect murine intestinal cells and, secondly, that it can transfect human gastrointestinal mucosal/epithelial cells. Without being able to efficiently transfect gut cells, any oral application would not be possible, so it is essential to complete these studies prior to progressing any further with this initiative. The completion of these additional studies will not be at a significant cost to the Company and will not detract from the Company's existing workstreams.

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

"Our focus remains on the optimisation of the formulation and the continued generation of data for Nuvec®'s use as an injectable delivery system for vaccines and cancer treatments and we are pleased with the progress made to date and look forward to building on this and accelerating the work programme as the lock down continues to ease.

"Our research has indicated that certain characteristics of Nuvec® could make it particularly well suited as a delivery system for oral vaccines. The ability to demonstrate potential for success in this area would give us a very clear and strong competitive advantage over other delivery systems which are less suited for oral delivery of vaccines.

"As our work streams become more defined, so do our learnings from each, including how they can enhance the work moving forward. As our knowledge grows so does our ability to assess and pursue the opportunities that give us what we believe to be the greatest competitive advantage and our quickest route to commercial success."

Enquiries:

N4 Pharma Plc
Nigel Theobald, CEO — Via Scott PR

Allenby Capital Limited — Tel: +44(0)20 3328 5656
(Nominated Adviser and Joint Broker)
James Reeve/Asha Chotai

Turner Pope Investments (TPI) Limited — Tel: +44(0)20 3657 0050
(Joint Broker)
Andy Thacker

Scott PR Tel: +44(0)1477 539 539
Georgia Smith

About N4 Pharma

N4 Pharma is a specialist pharmaceutical company developing a novel delivery system for cancer and vaccine treatments using its unique silica nanoparticle delivery system called Nuvec®.

N4 Pharma's business model is to partner with companies developing novel antigens for cancer and vaccine treatments to use Nuvec® as the delivery vehicle to get their antigen into cells to express the protein needed for the required immunity. As these products progress through pre clinical and clinical programs, N4 Pharma will seek to receive up front payments, milestone payments and ultimately royalty payments once products reach the market.

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