N4 Pharma plc

N4P has announced the raising of additional development capital amounting to c.£2.03m (gross) from a placing of c.50.7m new ordinary shares at a price of 4.0p each. Significantly, the Group's unique silica nanoparticle delivery system, Nuvec®, has already demonstrated that is capable of loading and transfecting both DNA and mRNA and producing an immune response. Focus now is on a phased work program designed to make Nuvec® more consistent, easier to handle and therefore more efficacious. While N4P's virtual model and contracted laboratories have ensured its testing schedules have not been significantly hindered by the lockdown, the COVID-19 Pandemic has nevertheless provided it with an ideal opportunity to demonstrate how Nuvec® could substantially enhance delivery of a potential Coronavirus vaccine, as well as developments of other viruses that may well surface in the future. Having already demonstrated improved product consistency along with a significant data pack that is currently being generated from *in vitro* testing ahead of a still anticipated second half move to *in vivo* models, N4P appears ideally placed to commence licensing discussions with prospective partners later this year. The new funds raised will further bolster its cash position which amounted to almost £1m at last December's year-end. While 2H 2020 operational burn is likely to ramp-up somewhat from the c.£75k/month seen during 2019, this is expected to be sufficient to satisfy working capital/project development needs, including proof of concept ('POC') works necessary to permit participation in a COVID-19 vaccine development programme(s) and progressing Nuvec® toward its first (partner-dependent) clinical trials collaboration, while also demonstrating GMP manufacturing scalability.

Significant development progress

To date, 2020 has been a busy and productive period for N4P. Milestones included:

- Using an improved manufacturing process, it successfully demonstrated that the Nuvec® particle can be effectively and repeatedly dispersed into a more monodisperse formulation, prior to the addition of DNA
- The signing of a 14-month research collaboration with Nanomerics Limited ('Nanomerics') to produce and test two candidate formulations.
- Undertaking a proof of concept research project using a COVID-19 DNA plasmid for demonstrating the ability of Nuvec® to be used as a delivery system by potential collaboration partners developing COVID-19 DNA or RNA vaccines.
- The appointment of Evotec International Gmbh ('Evotec'), the leading drug discovery alliance and development partnership company, to undertake the Nuvec® POC work for use with COVID-19 at its site in France.
- The filing of a new UK patent application around both Nuvec®'s ability to be used to manufacture viral vectors and to make viral vectors more efficient in applications such as ex-vivo gene therapy treatments.

Nuvec® is a novel nucleic acid delivery system

Nuvec® demonstrates significant promise as a non-viral delivery vehicle for DNA/RNA, with key advantages compared to lipid, other silica and viral systems, including high capacity loading and protection of nucleic acid. *In vitro* analysis suggests this functionalised silica nanoparticle is capable of localised *in vivo* transfection efficiency, through both subcutaneous and intratumoural routes, while remaining well tolerated at high doses with no induction of high levels of inflammatory cytokines. Offering an excellent safety profile, N4P is now focused on achieving Nuvec®'s formulation optimisation/stability and scalability along with COVID-19 proof of concept for delivery.

Stock Data

Share Price:	4.60p
Market Cap:	£7.0m*
Shares in issue:	152.2m*

**post Placing*

Company Profile

Sector:	Pharmaceuticals
Ticker:	N4P
Exchange:	AIM

Activities

N4 Pharma plc ('N4P, 'the Group') a specialist pharmaceutical company developing a novel silica nanoparticle delivery system for vaccines and therapeutics for licensing to pharmaceutical and biotech partners. This nanoparticle has the potential to help commercialise cancer immunotherapy drugs and improve the effectiveness of viral vaccines. Nuvec®, the Company's lead development is a unique, non-viral adjuvant delivery system that has the potential to revolutionise vaccines and cancer treatments.

Share price performance

Source: LSE

Past performance is not an indication of future performance.

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Strategic Vision

The use of DNA and RNA in the life science sector is a major growth area. One aspect that has become a consistent theme in discussions related to therapeutic potential, however, centres on the need for a safe and effective delivery system. Nuvec® has already demonstrated its ability to provide such a solution. The successful conclusion of its current chemistry, manufacturing and control ('CMC') modelling along with commencement of *in vivo* efficacy studies, could potentially create an attractive alternative to existing solutions being used in this area.

N4P's strategic vision is to build a sustainable drug delivery company that creates better outcomes for patients, while generating value for partners and investors by leveraging its unique Nuvec® technology in order to develop innovative vaccines and cancer treatments. Nuvec® nanoparticles can be loaded with a wide range of nucleic acids and deliver them into cells to generate the required antigen protein expression. The Group's focus has been and remains on DNA/RNA cancer vaccines and treatments, through which it identifies multiple partnership opportunities for its platform, although the COVID-19 Pandemic has more recently presented new opportunities to showcase Nuvec®'s enhanced delivery potential for a prospective Coronavirus vaccine(s).

The Group's business model centres on the development of novel versions of vaccines and cancer therapeutics in partnership with major biotech or pharmaceutical companies using its Nuvec® delivery system. Its proposal is to license Nuvec® for upfront, milestone and ultimately royalty payments. This creates opportunity for the relatively early collection of a series of different staged fees across multiple partnered platforms, with a view to avoiding the costs and extended duration otherwise implied for N4P's peers that chose to independently enter phased clinical trials for their therapeutic developments.

Use of Proceeds

The oversubscribed equity Placing announced yesterday, raises a total of £2,029,250 and utilises all of the Group's existing share authorities. It will represent approximately 33.33 per cent. of the enlarged issued share capital of the Group.

In additional to general working capital purposes, the net funds raised from the Placing will be used to fund the following specific areas:

1 Proof of concept research on the COVID-19 plasmid DNA project

To accelerate this proof of concept project and will include the following key activities:

- Establish and validate detection assays for the COVID-19 protein
- Conduct cell-based assays to confirm whether Nuvec® can bind the plasmid, transport it into cells and effect efficient production of the COVID-19 protein
- Undertake *in vivo* experiments once cell-based results are available. Positive *in vivo* results would indicate that Nuvec® has the potential to provide an effective platform for the development of a human COVID-19 vaccine
- Investigate GMP formulation and manufacture of a vaccine containing Nuvec® loaded with the COVID-19 DNA plasmid

2 Manufacturing of the Nuvec® nanoparticle

Small-scale manufacturing of Nuvec® has been successfully and repeatedly established in a development laboratory. To supply immediate needs and prepare for collaborations with partners new funding will also be used for the following activities:

- Technology transfer to a commercial manufacturer to provide multi-gram scale quantities of Nuvec®

- Further optimisation of the chemical processes involved in manufacture to facilitate scale production of Nuvec®
- Develop pharmaceutical quality processes and clinical GMP readiness to support fast use of Nuvec® by a partner in developing a human vaccine

3 Use of Nuvec® in viral vector manufacture.

Preliminary data has shown that as little as 5µg of a triple plasmid can yield high lentivirus titres when combined with Nuvec®. New funds will also be used for the following activities:

- Further optimisation of the titres achievable when using Nuvec® loaded with triple plasmids for lentivirus manufacture
- Comparative analysis of how Nuvec® compares to existing reagents using low levels of initial plasmid

Work Programmes - 2020 Planning Largely Unaffected by the Pandemic

As might have been expected, the final stage of work originally planned for Q1 2020, that of overseeing Nuvec®'s improved DNA loading process, has slipped somewhat due to the lockdown, however, the scheduled work for N4P is ongoing and it is realistic to expect its completion before end H1 2020. This follows January's announcement that the first two phases of this work had been successfully completed, with alterations to the manufacturing process, demonstrating improved dispersion of Nuvec® and how best to measure this dispersion. The remaining phase is designed to investigate how to add the DNA whilst maintaining this improved dispersion.

As was announced on 25 March 2020, N4P secured access to the plasmid DNA encoding for the spike of COVID-19, which is being used by major pharmaceutical companies that are focused on developing a vaccine for the new coronavirus. The Group went on to detail at its 23 April AGM exchanges, *in vitro* testing of improvements scheduled for Q2 2020 has been switched to COVID-19 spike plasmid (rather than using the reference standard plasmid DNA expressing Ovalbumin ('pDNA')), as has the scheduled Q3 2020 *in vivo* work that is designed to test for improved transfection and immune response.

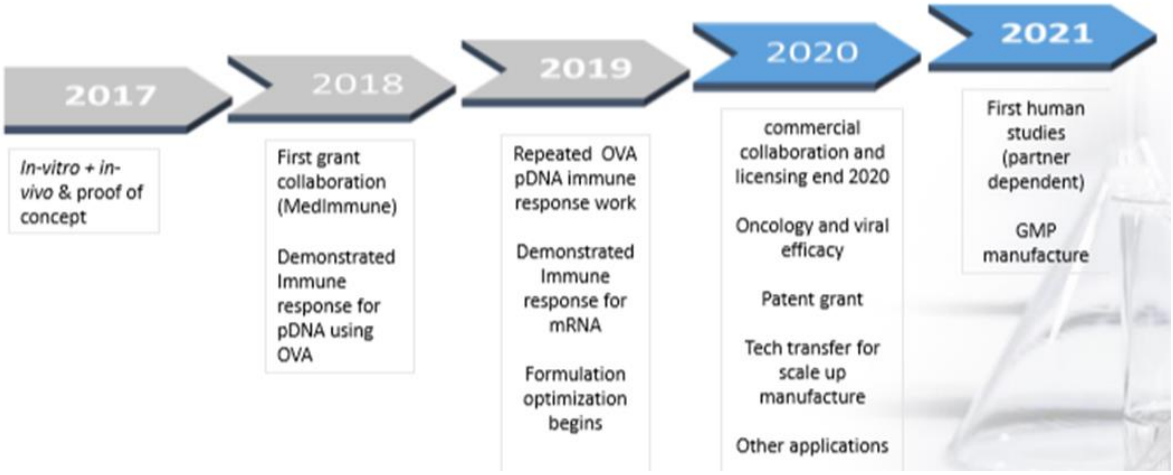
Assuming this changed medium does successfully demonstrate Nuvec® enhanced delivery, then it will not necessarily require the exercise to be repeated using Ovalbumin, although and final decision will await detailed examination of the data produced.

Assuming also that N4P's research partner, Nanomerics Limited, with which in February it announced two phases of a collaboration spread over 14-month,s shortly also recommences work within government guidelines, the efficacy studies should also remain on track for the current year. Based on these minor alterations, TPI now sees an updated 2020 schedule of remaining deliverables as follows:

- **Q2 2020 - Nuvec® improved DNA loading process**
- **Q2 2020 - *in vitro* (COVID-19 spike) testing of improvements**
- **Q2-Q3 2020 - *in vivo* (COVID-19 spike) testing of improved transfection and immune response**
- **Q3-Q4 2020 - conduct *in vivo* coronavirus model**

Assuming a successful conclusion to this program of work, the Directors believe the subsequent data pack and improved consistency will put the Group in a much stronger position to embark on licensing discussions with prospective partners.

Nuvec®: Key Milestones and Targets



Source: N4 Pharma

Nuvec® Opportunity

Improvements in DNA and RNA technology are leading to a significant increase in the number of related treatments in development, along with expression of substantial investor interest. One example is Moderna Therapeutics, Inc. (NASDAQ:MRNA), which listed in 2018 IPO as the largest biotech offering in US history, raising over US$600m to then value the start-up at US$7.5bn. Its medical treatments, which are based on messenger RNA, are still relatively early in their phased human trials, which include cancer treatments as well as a vaccine for cytomegalovirus, or CMV, supported through 50:50 profit sharing agreements with both AstraZeneca and Merck. Belief in the company's core scientific developments means that it has successfully raised more over US$4 billion through partnerships and investments since its inception in 2009. Another that highlights the value of core technologies such as Nuvec®, might be the collaboration between Alexion Pharma and nanotechnology company Arbutus in 2017, which included terms of US$7.5m upfront plus up to US$75m in milestone payments in the context of Alexion's rare disease program.

N4P's own research efforts are focused on nucleic acid delivery in the human body. While nucleic acids demonstrate great promise as potential prophylactic vaccines or treatments for cancer and other diseases, their key complexity is that they are difficult to formulate as drugs. As such, development of an effective nanoparticle delivery system remains central to enabling their effective use in a therapeutic setting. Nuvec®'s unique functionalised silica nanoparticle design is potentially ideal for nucleic acid cellular delivery and overcomes many existing limitations.

Nuvec® - A solution for successful delivery of nucleic acids

There are three key aspects that need to be overcome in order to achieve successful delivery of nucleic acids:

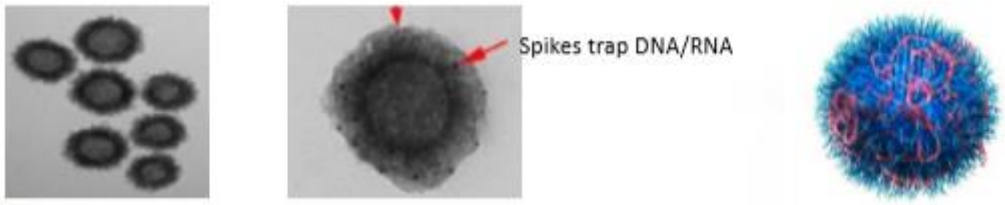
1. Protecting nucleic acids against digestion by nucleases in extracellular and intracellular space;
2. Transporting a negatively charged, hydrophilic molecule across the negatively charged, hydrophobic cell and nuclear membrane; and
3. Ensuring immunogenicity of vaccine products

Initial attempts to deliver nucleic acids to target cells focused on viral systems, which have high delivery efficacy, but appear to be limited in utility due to toxicity concerns. Alternatively, Electroporation, the action or process of introducing DNA or chromosomes into bacteria or other cells using a pulse of electricity to briefly open the pores in the cell membranes, has been seen to be relatively effective but particularly costly along with the observation of certain side effects. Lipid nanoparticles ('LNPs') have also emerged as an alternative to viral vectors, especially for mRNA applications, but these also come with several significant disadvantages including, cell toxicity and stimulating the release of systemic inflammatory cytokines along with liposome accumulation in the liver and spleen, potentially resulting in hepato-toxicity and low drug payload for hydrophilic molecules.

In order to overcome such problems, N4P is developing a new functionalised silica nanoparticle as a more efficient drug delivery vector for nucleic acid payloads. Nuvec® nanoparticles are hollow silica spheres covered in thin silica structures functionalised with polyethyleneimine ('PEI') to enhance binding of macromolecules. Such nanoparticles can be manufactured in a controlled manner to range from 80–500 nm in size, with standard Nuvec® nanoparticles being of c.180nm diameter.

The unique surface structure of Nuvec® nanoparticles provides a large surface area that traps and protects the looped structure of oligonucleotides, such as siRNA, DNA, mRNA, and others. As such, Nuvec® has been designed to deliver nucleic acids directly into cells and to overcome many of the weaknesses of lipid and viral delivery systems. A video animation to see Nuvec® in action can be viewed here.

Microscopic Images together with Graphic Model of Nuvec®



Source: N4 Pharma

COVID-19 proof of concept

In March, N4P announced it was undertaking a POC) research project using a COVID-19 DNA plasmid for the purpose of showcasing Nuvec®'s ability to be used as a delivery system by potential collaboration partners developing COVID-19 DNA or RNA vaccines.

Specifically, the POC work will show whether Nuvec® is capable of loading the COVID-19 plasmid and transfecting cells with the plasmid *in vitro*. Assuming successful *in vitro* transfection, N4P will then undertake a POC *in vivo* study to demonstrate the improved transfection when using Nuvec®, compared to not using the delivery system, by measuring the production of the antigenic protein and antibodies generated against the encoded COVID-19 protein.

Having received an initial quantity of the COVID-19 spike plasmid DNA from the National Institute for Health ('NIH') in the USA, N4P appointed Evotec International Gmbh (EVT.DE) to undertake the POC work for use with COVID-19 at its site. Initial POC work has already commenced with a view to examining the following three stages:

1. **Amplification of the plasmid DNA received from the NIH to provide sufficient plasmid DNA to undertake the *in vitro* and initial *in vivo* studies. This work is expected to take approximately four weeks;**
2. **Demonstrating whether Nuvec® is capable of loading the COVID-19 plasmid and transfecting murine peripheral blood mononuclear ("PBMC") cells *in vitro* and induce an expression of the spike protein in target cells. This stage is expected to last a further ten weeks; and**
3. **Subject to positive results being achieved at stage 2, undertaking an initial pre *in vivo* study to demonstrate expression of the spike protein in target cells in a murine target. This stage would be expected to take a further ten weeks, commencing in mid-July.**

Once the stage 3 results have been reviewed, N4P will then determine whether to do a further *in vivo* study to demonstrate the capability of Nuvec® to generate COVID-19 specific antibodies. In light of the current global urgency around treatments for COVID-19, the Group would also seek to collaborate, where it can, with appropriate partners to accelerate further studies at this juncture.

Further to this, on 24 April 2020, N4P announced the filing of a new patent which focussed on how Nuvec® can be used to make viral vectors (see below) more efficient. With the prospect of a COVID-19 vaccine nearing, the industry is rapidly shifting its focus to manufacturing capacity and ensuring the vaccine can be produced at scale, fast and safely.

Multiple Nuvec® applications

Numerous opportunities exist for such a novel delivery system to deliver innovative new vaccine and therapeutic products using nucleic acids, as detailed below. Beyond these, possible additional uses also include delivery of peptides, production of viral vectors, small molecule use, etc.

Identification of Multiple Potential Applications for Nuvec®

Applications	Benefits	Market Size
Cancer treatments	Intratumoural injection of cancer-killing antigens for direct transfection of cells within the tumour	$121 bn global market 2017 ††
Cancer Vaccines	Delivers antigen expressing tumour protein to wake up body to the existence of the tumour and attack it	$2.5 billion in 2015 to $7.5 billion in 2022. 1,286 products in pipeline*
Prophylactic vaccines for hard to treat diseases such as influenza, zika, ebola	Delivery of virus antigen to produce antibodies to build immunity to virus	$32 bn global market in 2015 rising to $77bn by 2024 †

Source: N4 Pharma

*Global Cancer Vaccines Market to 2022, GBI Research
,†Million insights apr2018/9 ††Therapies for Resistant and Recurrent Metastatic Cancer, November 2017

New opportunity for use in manufacture of viral vectors

Whilst investigating the dispersion of Nuvec® to improve its *in-vivo* consistency, N4P also undertook research covering *in vitro* applications of Nuvec®, based on the fact that all data had demonstrated good and consistent loading and transfection based on the molecule's use. As a result, in April 2020, N4P filed a new UK patent application around both Nuvec®'s ability to be used to manufacture viral vectors and to make viral vectors more efficient in applications such as *ex vivo* gene therapy treatments.

This opportunity is based on the fact that Nuvec® has a unique structure that allows the easy loading of DNA plasmids. The manufacture of viral vectors typically requires the use of two or more plasmids; Nuvec® has been shown to be capable of loading multiple plasmids. In recent research conducted by N4P, it has been demonstrated that loading Nuvec® with the three plasmids typically used to produce lentivirus, resulted in an increase in the amount of the desired viral vector produced. The manufacture of viral vectors is an expensive and exacting process, so utilising Nuvec®'s ability to efficiently load and deliver multiple plasmids holds potential to greatly reduce the costs involved.

As detailed above, an important use of viral vectors is in *ex vivo* gene therapy. In this approach, a patient's cells are taken from their body and more are grown in the laboratory. Whilst still outside the body, these cells are modified by adding the gene of interest into the cells' DNA by using viral vectors that are carrying the gene. These cells, carrying the gene designed to treat the patient, are then re-inserted back into the patient's body. In separate research, the Group has demonstrated that when complexed with a lentivirus carrying a gene of interest, Nuvec® can be used as a reagent to produce cells containing the gene using a fraction of the original lentivirus, thereby suggesting that this process can be made cheaper and more efficient. The Company is now working with external consultants to identify how best to enter the virus manufacture and *ex vivo* gene therapy markets.

The global viral vector manufacturing market was valued at US$273 million in 2017 and is projected to grow to a value of US$816 million by 2023. Sales of transduction reagents were estimated to be US$68m in 2017, expanding to US$123m by 2024. These are both significant markets for in-vitro applications of Nuvec® and available as additional commercial opportunities, while N4P continues to develop its *in-vivo* data package for licensing the nanoparticle as a delivery system for cancer treatments and vaccines.

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