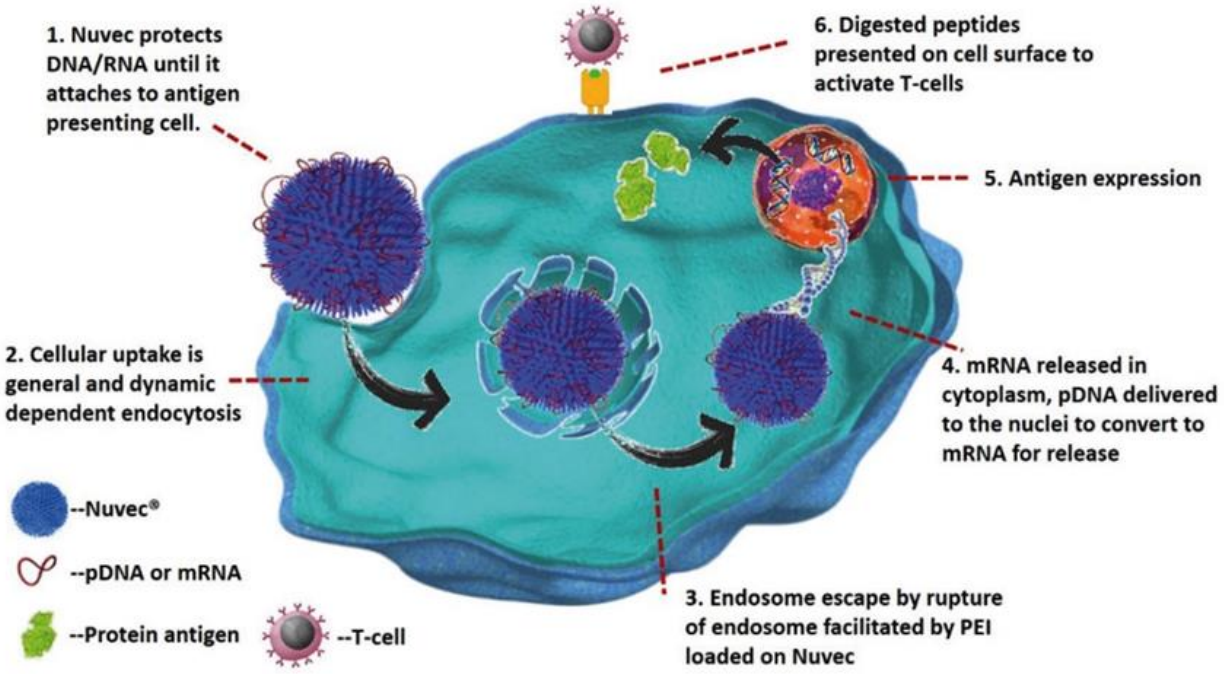
SP Angel Healthcare
N4 Pharma
Initiation of Coverage
18th November 2020



Source: N4 Pharma

SP ANGEL
Non-Independent Research
MiFID II Exempt

** SP Angel acts as Nomad and Joint Broker to N4 Pharma, and therefore this information should be viewed as a Marketing Communication.*

18th November 2020

Stock Data

Ticker	N4P.L
Share Price:	6.5p
Market Cap:	£10.1m

Source: Bloomberg (prior trading day's close)

Company Description

Biotechnology business focused on the development of Nuvec®, a silica nanoparticle-based delivery system for nucleic acid-based vaccines.

Share Price Chart (p)

Source: Bloomberg

Healthcare Research

Vadim Alexandre
vadim.alexandre@spangel.co.uk
+44 20 3470 0532
Liam Gascoigne-Cohen
liam.gascoigne-cohen@spangel.co.uk
+44 20 3470 0530

Sales

Rob Rees
+44 20 3470 0535
Abigail Wayne
+44 20 3470 0534
Richard Parlons
+44 20 3470 0471
Grant Barker
+44 20 3470 0471

Initiation of Coverage

N4 Pharma*

AIM: N4P *CORP

Nuvec®: Looking to deliver

Key points

- **Novel vaccine delivery platform:** N4 Pharma ('the Group', 'the Company', 'N4P') is focused on the development of Nuvec®, a silica nanoparticle-based system for the delivery of nucleic acid-based vaccines and therapies. The platform offers an alternative delivery method to conventional systems. Potential benefits include an improved safety and tolerability profile, a simple manufacturing process with rapid scale-up potential, and biological stability. N4 Pharma has performed multiple *in vivo* and *in vitro* tests which demonstrated that Nuvec® loaded with plasmid DNA (pDNA) and messenger RNA (mRNA). can stimulate an immune response.
- **COVID-19 project in the final stage:** The COVID-19 pandemic has put the use of DNA/RNA-based vaccines into the spotlight. N4P is initiating a study to evaluate whether Nuvec® loaded with DNA encoding a SARS-CoV-2 antigen can generate COVID-19-specific antibodies in mice. Although N4P is not looking to develop a COVID-19 vaccine itself, the successful completion of this project would demonstrate to potential partners the use of Nuvec® as a delivery system and provide valuable data in a high-profile indication.
- **Opportunities in other applications:** The Group is expanding the potential applications for Nuvec® outside traditional vaccine delivery to provide further market opportunities for the system. The Group has identified potential for Nuvec® as an oral vaccine delivery system and is undertaking initial proof-of-principle work in this area. Oral vaccination is a novel administration route which could offer advantages over conventional injection-based vaccine delivery. N4P also recently outlined a new programme to test the use of Nuvec® for the delivery of gene silencing cancer therapies. Should the evaluation programme be a success, it could unlock an additional commercial opportunity for the Nuvec® platform.
- **Optimisation work progressing**: N4P continues to conduct studies to further understand the activity of the Nuvec® platform and enhance its potential for nucleic acid delivery. The Company has worked with Evotec and the Centre for Process Innovation to optimise the molecule and is currently working with Nanomerics, a nanoparticle specialist. Nanomerics is supporting a programme that aims to increase the reliability of the platform to generate a consistent response in both *in vivo* and *in vitro* testing. An *in vivo* study using Nuvec® generated from the optimisation programme is expected to commence in early 2021.

Outlook: N4 Pharma is well-positioned to offer developers an alternate delivery approach for their DNA/RNA-based vaccine candidates. Supported by cash from a placing in May, N4P is nearing completion of its COVID-19 programme. Positive results from this project would be a significant milestone for the Group. Through the optimisation programme N4 Pharma looks to progress Nuvec® to a stage where it can seek licencing agreements. We expect interest from potential partners seeking to use Nuvec® as part of their development programme for nucleic acid-based products.

Year-end Dec	2017A	2018A	2019A	H120A
Revenue (£m)	0.11	0.07	-	-
Pre-tax Profit (£m)	(1.93)	(1.39)	(0.95)	(0.59)
Net Cash/(Debt) (£m)	1.33	0.79	0.97	2.44
Basic EPS (GBp)	(1.26)	(1.32)	(0.87)	(0.48)
Diluted EPS (GBp)	(1.24)	(1.30)	(0.87)	(0.47)

Source: Company reports; SP Angel forecasts

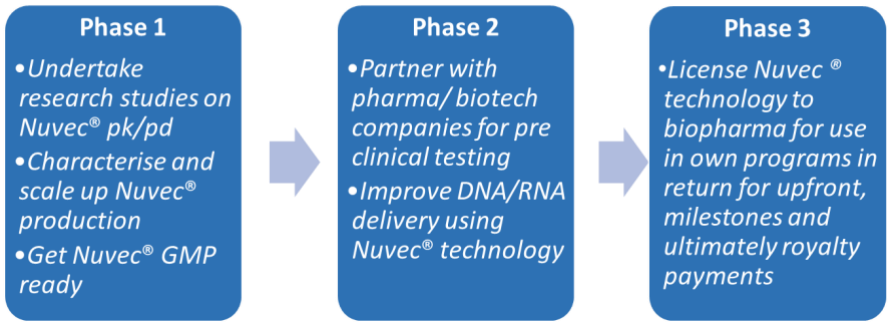
Investment Thesis

Nuvec® platform offers multiple licencing opportunities

N4 Pharma is focused on developing Nuvec® into a platform which can improve vaccine efficiency, minimise side effects and reduce end-user costs. The Group continues to optimise the platform and, once an appropriate level of data has been completed, N4 Pharma seeks to engage in partnering discussions. The Group expects prospective partners would look to license Nuvec® to support the development of their own nucleic acid-based products. By focusing on licencing agreements related to the use of Nuvec® in specific therapy programmes, the Group retains the freedom to strike licencing deals with other developers for different indications. This offers scope to achieve multiple licencing agreements and increase income generation from the platform.

Nuvec® business model

Multiple opportunities for different versions of Nuvec® in different sectors



Source: N4 Pharma

Operating in the high growth area of DNA/RNA vaccines

DNA/RNA vaccines have potential advantages over other approaches, such as a robust safety profile and a simple manufacturing process with rapid scale-up potential. The COVID-19 pandemic has accelerated interest in the area. The presence of DNA/RNA-based COVID-19 vaccines in late-stage trials demonstrates the speed at which these vaccines can be developed to respond to a disease outbreak. The encouraging interim readouts from the Phase 3 trials testing Pfizer and Moderna's mRNA-based vaccine candidates highlights the efficacy of DNA/RNA vaccines (Both Pfizer and Moderna's candidates had a vaccine efficacy rate of over 90%). As a delivery system which aims to improve nucleic acid delivery, Nuvec® is well-positioned to capture interest in this growing area.

Demonstrated ability to generate an immune response

N4 Pharma has performed *in vitro* and *in vivo* tests which have demonstrated that Nuvec, loaded with DNA/RNA encoding an antigen, can generate both a humoral and cellular immune response to the target antigen. The ability to stimulate both forms of the adaptive immune response is an essential driver in developing protective immunity, the key focus of any vaccine. The Group is looking to build on these findings via its COVID-19 proof-of-concept research project and optimisation programme.

COVID-19 project generating data in a high-profile indication

Having previously demonstrated that Nuvec®, loaded with pDNA encoding for Ovalbumin protein (a test antigen), can generate an immune response, the Group is looking to replicate these findings in a COVID-19 proof-of-concept study. The objective of this project is not to fully develop and commercialise a COVID-19 vaccine, but to demonstrate the utility of the Nuvec® platform in a high-profile area. The Group has successfully demonstrated that Nuvec® loaded with pDNA encoding the SARS-CoV-2 Spike protein can transfect human cells *in vitro*. An ongoing experiment is now testing whether Nuvec® loaded with pDNA encoding the SARS-CoV-2 Spike protein can elicit an antibody response in mice. The successful completion of the COVID-19 project, in combination with previous work with Ovalbumin protein, would provide potential partners with additional data regarding the value of Nuvec® as a delivery system for nucleic acids and should support future efforts to strike licencing agreements.

Nuvec® optimisation programme is progressing well

Having demonstrated an ability to stimulate an immune response, the Group is advancing a programme to increase the reliability of the platform to generate a consistent response in both *in vivo* and *in vitro* testing. Earlier in 2020, the Group struck a collaboration with Nanomerics, a nanoparticle specialist, who are performing formulation work to optimise the platform. The partnership is progressing well, with initial studies demonstrating that Nuvec®, loaded with pDNA, can be dried, stored at room temperature and reconstituted without any degradation of the pDNA payload. This would be a significant feature for the platform as current technologies require cold-chain storage (Pfizer/BioNTech's COVID-19 vaccine has to be stored at -70°C). The optimised formulation is now being tested *in vitro* to evaluate if cell transfection has been maintained. An *in vivo* study using Nuvec® generated from the optimisation programme is expected to commence in early 2021.

Potential new applications in oral vaccines and cancer

Whilst N4 Pharma is primarily focused on the development of an injectable vaccine delivery system, the Group recently highlighted the potential use of Nuvec® in two new areas. N4P has initiated a programme to establish the viability of Nuvec® as an oral delivery system. This is running alongside existing workstreams with no impact on timings and limited additional costs. The use of oral vaccines could provide a cost-effective method for vaccination programmes, with an increased level of patient compliance. This could increase the effectiveness of vaccination programmes and reduce disease transmission. The Group is also evaluating the use of Nuvec as a delivery system for cancer therapies. In November, N4 Pharma outlined a new programme to evaluate the use of Nuvec® as a delivery system for nucleic acid-based therapies with anticancer potential. The Group has appointed Nanomerics, who are currently conducting the optimisation programme, to complete a preclinical proof of concept study. The programme is expected to commence imminently and is expected to take up to twelve months. Should the evaluation be a success it could unlock an additional commercial opportunity for the Nuvec® platform.

Peer group analysis

We estimate that N4 Pharma's breadth of IP and the wide applicability of their delivery system is not fully captured by its current valuation.

We compared N4 Pharma to a number of London-listed, early stage drug development companies. N4 Pharma's £10.4m market capitalisation is well below the £54.4m median market capitalisation for the group, corroborating our view.

Peer-group analysis of AIM or LSE Standard-listed companies

Name	Ticker	Mkt Cap
Median		**54.4**
N4 Pharma Plc	**N4P LN**	**10.4**
Hemogenyx Pharmaceuticals Pl	HEMO LN	37.3
C4x Discovery Holdings Plc	C4XD LN	50.9
Sareum Holdings Plc	SAR LN	48.8
E-Therapeutics Plc	ETX LN	54.4
Okyo Pharma Ltd	OKYO LN	54.6
Redx Pharma Plc	REDX LN	125.0
Scancell Holdings Plc	SCLP LN	59.5
Silence Therapeutics Plc	SLN LN	359.9
Midatech Pharma Plc	MTPH LN	16.7

Source: Bloomberg

Competitors/Peers

There are few competitors which are developing nanoparticle delivery systems for nucleic acids. Arcturus Therapeutics (ARCT.NQ) has developed LUNAR, a lipid nanoparticle delivery system for nucleic acid. The clinical stage company has collaborations with five partners, who are using the system in multiple indications, such as COVID-19. These agreements include a 2017 collaboration with Johnson and Johnson with an undisclosed upfront fee and up to US$56.5m in conditional milestone payments plus sales royalties.

On AIM, Midatech Pharma (MTPH.L) is developing multiple therapy delivery platforms, including Q-Sphera™, a polymer-based therapeutics delivery system. Midatech has struck two collaboration agreements to investigate the use of Q-Sphera with different therapies. This includes a deal with Dr Reddy's Laboratories Ltd (RDY.NY), a large generic drug manufacturer. Ichor Medical Systems (Private) is developing the UNITE platform, an automated device for electroporation-mediated nucleic acid administration in humans. Ichor has struck agreements with Scancell (SCLP.L) and Immunomic Therapeutics (Private) to support the delivery of DNA vaccine candidates for COVID-19 developed by its partners.

SP Angel | Prince Frederick House | 35-39 Maddox Street | London | W1S 2PP | United Kingdom

Company Overview

Company Summary

N4 Pharma is a specialist pharmaceutical company that is developing Nuvec®, a novel silica nanoparticle designed to be a platform for the delivery of nucleic acid-based vaccines. The Company has generated promising preclinical data for Nuvec®. It aims to further optimise the platform before initiating discussions for potential licencing agreements with cancer and vaccine development companies who can use Nuvec as a delivery agent for their own therapeutic programmes.

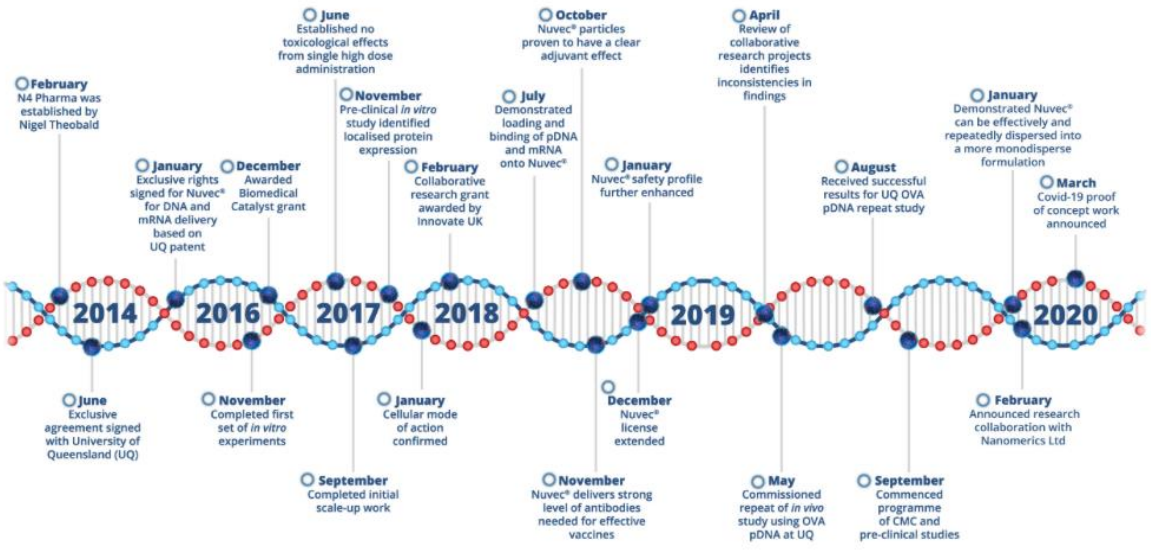
History

The Company was founded in 2014 by Nigel Theobald, current CEO of N4 Pharma. N4P acquired the exclusive rights to commercialise two of the University of Queensland's patent applications regarding the manufacture and use of silica nanoparticles as a platform for vaccine delivery. These patents cover the core IP surrounding the Nuvec® platform and the Group has been focused on developing Nuvec® to a commercial stage.

In January 2016, the Company gained further exclusive rights surrounding the use of Nuvec® as a delivery system for use in DNA and mRNA vaccines and therapeutics. In December of the same year, N4P received a Biomedical Catalyst grant to demonstrate scaled up nanoparticle production. The initial scale-up work completed in November 2017. Over this period, N4 Pharma conducted multiple *in vitro* and *in vivo* studies regarding the safety profile of Nuvec® and its ability to induce the expression of proteins.

N4 floated on the AIM stock market in 2017. The deal raised £1.5m for additional patent applications and to progress the generic-drug reformulation side of the business. At this time, an *in vitro* study showed that Nuvec® particles were effective in delivering pDNA to generate a localised protein expression. In 2018, N4P discontinued the generic-drug reformulation programme to focus on the continued development of Nuvec®. The Group generated additional data on the platform's safety profile and ability to generate an antibody response.

N4 Pharma company timeline



Source: N4 Pharma

Continued progress in 2020 despite the pandemic

At the start of 2020, N4P completed further optimisation work on Nuvec® and signed a research collaboration deal with Nanomerics Limited to produce and test two formulations using the Nuvec® delivery system.

Since the onset of the COVID-19 pandemic, N4 Pharma has initiated a project to investigate and demonstrate the utility of Nuvec® in delivering a nucleic acid-based vaccine candidate against SARS-CoV-2. This project aims to demonstrate the utility of Nuvec® to potential partners in a high-profile indication. The project has been progressing well, with promising *in vitro* data showing that Nuvec®, loaded with SARS-CoV-2 pDNA, can induce expression of the SARS-CoV-2 Spike protein in human cells. The Group is now looking to repeat these findings in a mouse model and look for the expression of antibodies against the Spike protein, which would indicate an immune response. Although N4P is not looking to develop a COVID-19 vaccine, the completion of this project would demonstrate to potential partners the use of Nuvec® as a delivery system.

The Group is also investigating two other applications of Nuvec®: The use of the platform to deliver cancer therapies, and its use as an oral delivery system. In both cases, Nuvec® has the potential to provide advantages over current techniques and progress in these areas could unlock additional commercial opportunities for the platform**.**

Placing in May 2020 to raise £2m

As mentioned, N4 Pharma began its COVID-19 proof of concept research in March 2020. Having secured access to SARS-CoV-2 plasmid DNA to enable the initiation of the project N4 Pharma subsequently undertook a placing in May to raise £2.1m. The primary use of funds included:

1. Acceleration of the proof of concept research on the COVID-19 plasmid DNA project;
2. Manufacturing of the Nuvec nanoparticle, including technology transfer to a commercial manufacturer, optimisation of the chemical processes to facilitate large scale production and to develop pharmaceutical quality practices and clinical GMP readiness;
3. Optimisation of the titres achievable when using Nuvec loaded with triple plasmids for lentivirus manufacture and comparative analysis with existing reagents using low levels of the initial plasmid;
4. General working capital purposes.

With funding secured, the Group has the resources to accelerate the proof of concept research on the COVID-19 project and push forward with manufacturing activities of Nuvec nanoparticle.

May 2020 Placing details

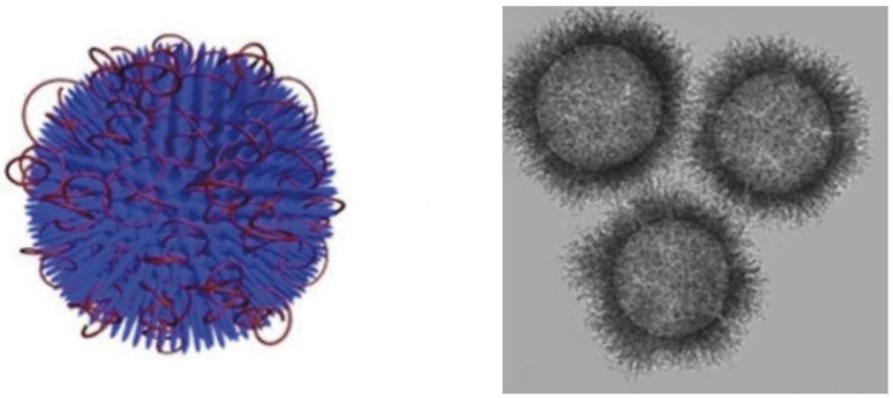
Placing	
Placing shares	50,731,250
Enlarged share capital	152,193,787
Fundraise price (p)	0.4
Fundraise proceeds (£m)	2.03

Source: N4 Pharma

Nuvec® Overview

Through Nuvec®, N4 Pharma aims to offer DNA or RNA vaccine developers a non-viral vector delivery system that can be used to carry a nucleic acid payload to the target site of action. A vital component of any vaccine system is the ability to safely deliver the payload to the target cell and generate an adequate immune response. This can lead to protective immunity if the individual is exposed to the pathogen.

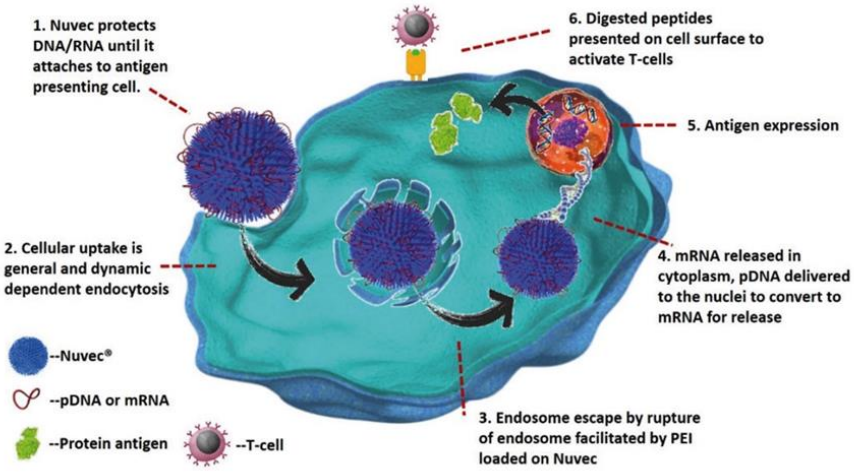
Nuvec® schematic showing nucleic acid molecules (red) trapped on the surface (left) and electron micrograph showing detailed structure (right).



Source: N4 Pharma

Nuvec has been designed for the optimal intracellular delivery of nucleic acids, such as plasmid DNA (pDNA) and messenger RNA (mRNA). The platform consists of silica-based nanoparticles which are hollow and are covered with silica spikes. The spikes contain polyethyleneimine (PEI), a polymer which provides a positive charge to support the binding of negatively charged nucleic acids to the particle. The nucleic acid is wrapped around the silica spikes which protect the payload until the particle reaches the target cell. The novel design allows larger volumes to be loaded, whilst protecting the payload from degradation as it travels to the target cell.

Nuvec mode of action



Source: N4 Pharma

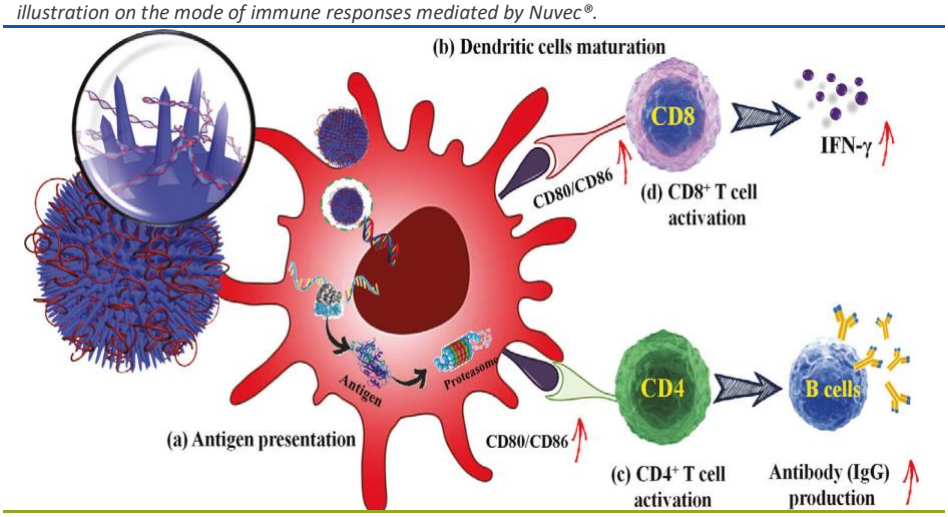
Nuvec® mode of action

Once the Nuvec® vaccine particle reaches the target, such as an antigen-presenting cells, the particle is internalised into the cell via a process known as endocytosis. This encapsulates the Nuvec® complex into a membrane-bound vesicle known as an endosome. The endosome has a more acidic pH level than observed in blood vessels. This pH change causes the PEI to change charge and the silica spikes to disintegrate. This releases PEI, which ruptures the endosome and releases the DNA/RNA payload into the cell cytoplasm. Depending on whether the payload is DNA or RNA-based determines the next step. If the payload is DNA-based, the nucleic acid is delivered to the nucleus, the part of the cell which carries most of the genetic information. Once in the nucleus, the pDNA is transcribed into mRNA, which is released into the cytoplasm and translated into the protein antigen.

Ability to generate a humoral and cellular immune response

Once the protein antigen has been synthesised, it is processed by the cell into a small peptide and presented on the cell surface. This enables the activation of the adaptive immune system to generate immune cells such as T and B-lymphocytes specific to the target antigen. Following this, memory T cells and circulating antibodies specific for the antigen remain in the individual. In the case of subsequent infection by a pathogen which carries the same antigen, i.e. the SARS-CoV-2 virus with the Spike protein, the immune response should demonstrate an improved ability to recognise and eliminate an infection.

illustration on the mode of immune responses mediated by Nuvec®.



Source: Yu C et al; Adv. Therap. 2020, 3, 1900154

Potential benefits of Nuvec®

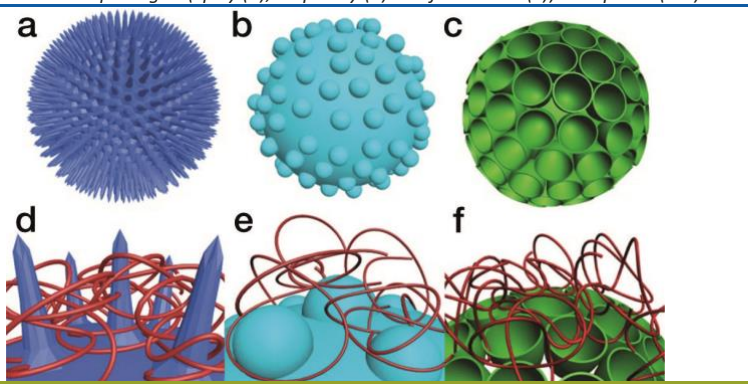
Whilst many RNA and DNA vaccine developers use lipid-based vaccine delivery systems, Nuvec® could offer an alternative platform with additional benefits, such as a higher safety profile and increased protection of the payload from degradation. *In vitro* and *in vivo* studies have shown Nuvec® demonstrates a strong safety and activity profile. Features of Nuvec® include:

1. **Safety profile:** Although safety studies have been limited to preclinical models, there has been no major toxicology issues observed for Nuvec®. As a silica-based particle, Nuvec® offers safety benefits over issues observed with lipid or viral based delivery platforms. As lipids are processed in the liver, the long-term use of lipid-based delivery systems may lead to liver injury. Silica is not thought to accumulate in the liver therefore Nuvec should not be susceptible to this issue and may be a better candidate for treatments which require repeat dosing. As Nuvec® is non-viral, there is no risk of recombination; whereby a viral vector combines with endogenous viruses to generate an active infection.

2. **Protection from degradation:** Nucleic acids are vulnerable to degradation by enzymes such as endonucleases. Therefore, it is vital that the vaccine delivery system protects the nucleic acid payload prior to reaching the target cell and soliciting antigen expression. The structure of Nuvec® is thought to provide adequate protection against degradation. An *in vitro* assay indicated that pDNA loaded on Nuvec® was entrapped at the base of the spikes rather than exposed on the outer surface where degradation by enzymes may be more likely. A further study demonstrated that Nuvec® protects against degradation of the payload pDNA and RNA by endonucleases.

3. **Storage at ambient temperatures:** An issue with nucleic acid-based therapies is the requirement to be stored at a cold temperature from manufacture to patient. Conventional subunit vaccines are stored at c.5°C but BioNTech and Moderna's COVID-19 vaccines require storage at -80°C and -20°C, respectively. The need for ultra-cold-chain storage may hinder commercial uptake for these therapies. Therefore, the ability to store nucleic acid therapies at ambient temperatures would be attractive to developers. Initial studies have demonstrated that Nuvec®, loaded with pDNA, can be dried, stored at room temperature and reconstituted without any degradation of the pDNA payload. Further testing is being conducted to assess if cell transfection is maintained.

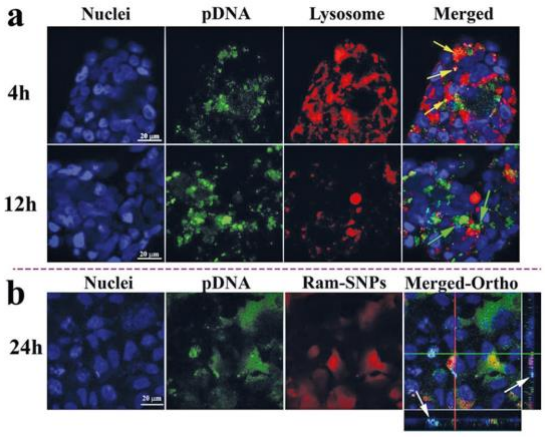
Different SNP morphologies (spiky (a), raspberry (b) and flower-like (c)) with pDNA (red)



Source: N4 Pharma

4. **Cellular delivery and transfection efficiency:** The ability for the vaccine to enter the target cell and solicit expression of the antigen protein by the cellular machinery is vital for subsequent immune system activation. When tested against different shaped structures of silica nanoparticles, Nuvec® was shown to deliver pDNA intracellularly whilst facilitating the highest cellular uptake. Further studies have shown that Nuvec is able to deliver both pDNA and mRNA into the cell's nucleus leading to protein expression after 24 hours.

Ability of Nuvec pDNA to enter nucleus; pDNA (green); Nuvec® (red); Nuceli (blue)



Source: N4 Pharma

5. **Loading capacity:** The amount of nucleic acid which can be loaded onto the delivery system determines the genetic information which can be delivered to, and subsequently expressed by, the host cell. The presence of silica spikes on Nuvec® increases the surface area available for the loading of a nucleic acid payload. pDNA loading capacity for Nuvec® was shown to be over 100 micrograms of pDNA per milligram of particle, or a plasmid containing 10k base pairs. Furthermore, Nuvec® has been shown to carry multiple DNA plasmids. The Group demonstrated that it was able to load Nuvec® with the three plasmids typically used to produce lentivirus, a commonly used viral vector for gene therapy. This opens a potential new market opportunity which uses Nuvec® to provide an alternate, lower-cost method to manufacture viral vectors.

6. **Immunogenicity:** The ability to stimulate a protective immune response to the target pathogen is the core focus of a vaccine. Studies using Nuvec® have demonstrated that Nuvec, loaded with an antigen, can generate antibodies specific to the target-antigen. Although at a preclinical stage, these studies demonstrate the ability of the platform to facilitate an immune repsonse. An ongoing *in vivo* study using COVID-19 antigens should provide further data regarding the immugenic nature of Nuvec®. Furthermore, research has indicated that silica nanoparticles, such as Nuvec® may have adjuvant-properties. This is an advantage, as an adjuvant techonology can enhance the immune response to a vaccine.

University of Queensland study and confirmation work

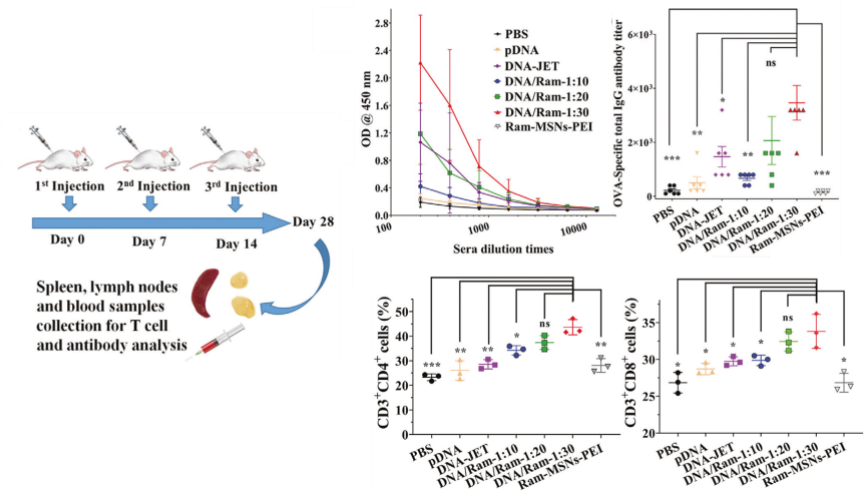
A study by the University of Queensland tested different variants of silica nanoparticles. The investigators found that the 'spiky' shape, as used in Nuvec® was the most promising candidate for a vaccine delivery system. In the study, the spiked silica nanoparticle exhibited the strongest binding affinity towards pDNA molecules, provided protection against degradation of the nucleic acid and facilitated the highest rate of intracellular gene expression across the morphologies tested.

2019 review and repeat testing

In April 2019, N4P undertook a review of the Nuvec® data from experimental studies conducted by both collaborators and CROs engaged by the Company. The Group found that there was variability between the protocols used by the Group's collaborators, CRO's and the original proof-of-concept work completed at University of Queensland. As a result, N4P commissioned the University of Queensland to perform additional studies with Nuvec® to generate, validate and document a methodology for the preparation and handling of Nuvec® prior to injection.

To achieve this, the University of Queensland repeated its original studies in mouse models using Ovalbumin, a standard test antigen. Mice were injected with Nuvec loaded with pDNA encoding for Ovalbumin at weekly intervals. The researchers tested different ratios of the number of pDNA molecules bound to Nuvec®. The study was a success, demonstrating that after three injections, Nuvec® can promote transfection and the production of antibodies specific to Ovalbumin, as well as the activation of a T-cell response. This study provided a benchmark protocol which can be used as a reference by CROs and collaborators for further *in vivo* studies on Nuvec® with different antigens as well as supporting manufacturing scale up.

Nuvec loaded with Ovalbumin pDNA (DNA/Ram-1) was able to generate an antibody (IgG) response and T-cell response (CD3+, CD4+, CD8+)



Source: Yu C et al; Adv. Therap. 2020

COVID-19 provides an opportunity to showcase Nuvec®

The development of an effective vaccine against SARS-CoV-2 is a key strategy to end the current pandemic. A vaccine is a treatment which stimulates the host's immune system to help it recognise and eliminate an infection. Since the first reports of the virus in 2019, there are considerable efforts underway to generate a vaccine with over 100 vaccine candidates in development. Nucleic-acid based vaccines have shown early promise in preventing COVID-19 infection. An RNA-based vaccine developed by Moderna Therapeutics (MDRNA.NQ) was the first candidate to enter the clinic in March 2020. In November, Pfizer and BioNTech were the first to post encouraging interim efficacy results from a Phase 3 trial testing BNT162b2, an mRNA-based COVID-19 vaccine candidate. Individuals vaccinated with BNT162b2 had a 90% reduction in expected COVID-19 infections versus subjects which received a placebo dose. Shortly thereafter, Moderna announced results that its own mRNA-based COVID-19 vaccine candidate, mRNA-1273, achieved a vaccine efficacy rate of 94.5% in its first interim analysis of a Phase 3 study. No serious safety concerns have been reported for either vaccine. With RNA/DNA vaccines at the forefront of the race to develop a vaccine for COVID-19, N4 Pharma is well-positioned in a rapidly growing market.

In March 2020, N4P outlined a proof-of-concept project to develop and test the use of Nuvec in a nucleic acid-based vaccine against COVID-19. The objective of this project is not to develop and commercialise a COVID-19 vaccine, but to demonstrate the utility of the Nuvec® platform in a high-profile area. The Group has already demonstrated that Nuvec® is capable of loading and transfecting both DNA and mRNA to elicit antibody production using Ovalbumin as a test antigen. The successful completion of the COVID-19 project, in combination with previous work, would provide potential partners with additional data regarding the value of Nuvec® and should support future efforts to strike licencing agreements.

Progress so far

Amplification of plasmid DNA

The project work commenced in May with the first stage involving amplifying plasmid DNA encoding for the SARS-CoV-2 Spike protein. This step was to ensure there was sufficient resources for testing in the studies. N4P received an initial quantity of plasmid DNA (pDNA) from the US National Institute of Health and appointed Evotec International, a leading CRO, to undertake the proof of concept work. By the end of May, the Group had successfully completed this initial stage.

In vitro transfection assay

With sufficient plasmid DNA available, N4 Pharma tested if the pDNA can be loaded onto the Nuvec® platform and if the combination can transfect and induce expression of the SARS-CoV-2 Spike protein in human cells *in vitro*. The researchers used Human embryonic kidney cells (HEK), a common cell line used in preclinical testing. In August, N4 Pharma announced that Nuvec®, loaded with SARS-CoV-2 plasmid DNA, can successfully transfect HEK cells *in vitro* and induce expression of the SARS-CoV-2 Spike protein in the HEK cells. The ability of Nuvec® to induce expression of the Spike protein *in vitro* was a positive step forward for the programme as it moves into *in vivo* testing.

In vivo pilot study

Upon the successful completion of the *in vitro* element, the Group performed a pilot *in vivo* study. Mice received a single injection of Nuvec® loaded with pDNA encoding the SARS-CoV-2 2 Spike protein and tissue samples were taken to determine the presence of SARS-CoV-2 antigen. No measurable quantity of SARS-CoV-2 Spike protein was observed in either the mice treated with Nuvec® or the experiment's positive control. This result was surprising given that a positive control is used to generate a known response for comparison to the experimental treatment. The Group expects that the plasmid used in this assay had a low expression profile which, combined with only a single injection, resulted in no detectable expression of protein. Rather than repeat this experiment, N4 Pharma moved to the next stage of the project whilst performing exploratory studies in parallel to understand the potency of the SARS-CoV-2 plasmid.

in vivo antibody study

Despite the lack of signal in the pilot study, N4 Pharma is progressing the project to a larger *in vivo* study. In this study, the Group is looking to inject Nuvec® loaded with the SARS-CoV-2 Spike protein pDNA into a mouse model. Mice are to receive up to three injections of Nuvec® at one-week intervals. The researchers will look for the presence of SARS-CoV-2 Spike protein as well as a COVID-19 specific antibody response. The study is expected to commence shortly. Positive results in this *in vivo* study would provide valuable preclinical proof-of-concept data regarding the ability of Nuvec® to stimulate an immune response.

After the proof of concept trial

As previously mentioned, N4 Pharma does not aim to develop a COVID-19 vaccine itself, however the successful completion of this project would demonstrate to vaccine developers that Nuvec® loaded with plasmid DNA is able to generate an immune response in animal models. We view this data to be of significant interest to potential partners both within the development of a COVID-19 vaccine as well as for the use of the delivery platform in other indications.

N4 Pharma COVID-19 proof-of-concept project

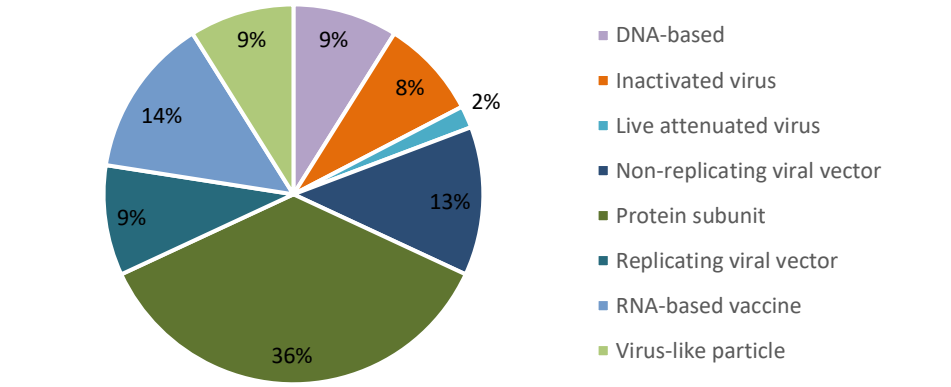
Stage 1	Stage 2	Stage 3	
Plasmid expansion Completed	In vitro study Completed	Pre in-vivo study Completed	Main in-vivo study Planned
Amplification of plasmid DNA	Successfully transfected human cells in vitro and induced expression of the spike protein in cells.	Injection of Nuvec into a mouse model to observe synthesis of the Spike protein – No spike protein observed in experiment (including positive control)	Animals to be injected 3x at weekly intervals to observe the number of injections required for the expression of antibodies.

Source: N4 Pharma

COVID-19 has accelerated interest in DNA/RNA vaccines

Nucleic-acid based vaccines have been highlighted as a rapid method to develop a COVID-19 vaccine. There are over 40 RNA or DNA-based vaccine candidates under development for the prevention of COVID-19 disease. Many have progressed to late-stage clinical trials including RNA-based vaccine candidates developed by BionTech/Pfizer and Moderna Therapeutics. These are frontrunners for the race to develop an approved vaccine with both companies targeting a potential US Emergency Use Approval decision before the end of 2020.

Breakdown of different classes of COVID-19 vaccine candidates (n=213)



Source: Milken Institute

DNA vaccine candidates for COVID-19

In terms of DNA-based vaccine candidates for COVID-19, there are currently five undergoing clinical trials. This includes INO-4800, developed by Inovio (INO.NQ) which is currently in Phase 2 trials. In June 2020, Inovio posted encouraging interim Phase 1 clinical data which showed that most subjects tested demonstrated both a neutralising antibody and a T-cell immune response. INO-4800 is delivered by electroporation via the Group's Cellectra 3PSP smart device. Takara Bio, a Japanese biopharma, has teamed up with Cytiva to develop a DNA based vaccine which is delivered by a jet injection device. The partners' vaccine candidate is in ongoing Phase 1/2 clinical trials.

There are a number of developers with nucleic acid-based vaccine candidates which are at the preclinical stage of development. Once the Nuvec® COVID-19 programme completes, the platform may be of interest to these parties to potentially enhance the activity and delivery of their vaccine. There are currently 14 DNA vaccine candidates at the preclinical stage. **Scancell (SCLP.L)** is developing a DNA vaccine which relies on the SARS-CoV-2 nucleocapsid (N) and S protein antigen to generate an immune response. Scancell looks to progress to Phase 1 trials in Q121. Cambridge-based **DIOSynVax (private)** recently received a £1.9m grant from the UK government to progress its DNA vaccine candidate, *DIOS-CoVax2,* into clinical trials (expected by early 2021). Similalry to Inovio, delivery of *DIOS-CoVax2* also relies on a jet injection device (the *PharmaJet Tropis Needle-Free* Injector).

List of clinical stage DNA/RNA vaccine programmes for COVID-19

Developer	Category	Development	Anticipated Next Steps	Product Description
Genexine Consortium/ Pohang University of Science and Technology/ Binex/ PT Kalbe Pharma	DNA	Phase I/II	Phase I/II study: Phase I began end of June 2020, preliminary data expected September 2020; Animal study results announced August 2020	DNA; (GX-19)
Inovio Pharmaceuticals/ Thermo Fisher Scientific	DNA	Phase I/II	FDA partial clinical hold for planned Phase II/ III trial reported on 9/28/2020; Phase I/IIa trial began July 2020; Animal study results released July 2020; Joined US Operation Warp Speed in June 2020; Phase I began April 2020, interim data of ongoing study released June 2020	DNA; (INO-4800) plasmid vaccine with electroporation
Osaka University/ AnGes/ Takara Bio/ Cytiva/ Brickell Biotech	DNA	Phase I/II	Phase I/II began end of June 2020, results expected during Q1 2021	DNA; (AG0301 & AG0302) plasmid vaccine + adjuvant
Zydus Cadila Healthcare	DNA	Phase I/II	Phase I/II study: Phase I began July 2020 and Phase II began August 2020, initial results expected September 2020	DNA; (ZyCoV-D) plasmid vaccine
Symvivo	DNA	Phase I	Phase I dosed November 2020	DNA; bacTRL-Spike
Moderna/ NIAID	RNA	Phase III	Phase III interim analysis results announced 11/16/2020; Swissmedic started rolling review on 11/13/2020; UK Medicines and Healthcare products Regulatory Agency (MHRA) started rolling review on 10/27/2020; EMA confirmed marketing authorization submission eligibility on 10/14/2020; Health Canada rolling submission initiated on 10/13/2020; Study protocol for late-stage clinical trials released September 2020; Phase I interim data from older adult cohorts released Aug 2020 and published Sep 2020; Phase III COVE study began July 2020, completed enrollment on 10/22/2020; Animal study results published July/Aug 2020; Phase I interim results published July 2020; FDA fast track designation granted May 2020; Selected for US Operation Warp Speed in April 2020	RNA; LNP-encapsulated mRNA (mRNA 1273)
BioNTech/ Pfizer	RNA	Phase II/III	Phase III interim analysis results announced 11/09/2020; Phase I data published October 2020; FDA approved late-stage trial enrolment of children 12 years and older in October 2020; EMA rolling submission initiated on 10/6/2020; Study protocol for late-stage clinical trials released Sept 2020; Amended protocol to FDA to expand trial enrolment to 44,000 participants; Phase IIb/III trial began Jul 2020; FDA granted Fast Track designation for BNT162b1 and BNT162b2 in Jul 2020; Selected for US Operation Warp Speed in Jul 2020; Phase I/II began Apr 2020; preliminary data released Jul 2020, additional data published Aug 2020 and Sept 2020; Animal study data released Sept 2020	3 LNP-mRNAs; BNT162
CureVac	RNA	Phase II	Phase IIb/III trial expected to begin by the end of 2020; Phase IIa trial began end of September 2020; Phase I trial began June 2020, interim results reported November 2020; Pre-clinical data released October 2020	RNA; mRNA (CVnCoV)
Arcturus/Duke-NUS/ Catalent	RNA	Phase I/II	Pre-clinical results released September 2020; Phase I/II began August 2020; Received approval to launch clinical trials in Singapore end of July 2020	LUNAR-COV19; RNA; mRNA
Imperial College London	RNA	Phase I/II	Pre-clinical results published July 2020; Phase I/II trial began June 2020	RNA; LNP-nCoVsaRNA
PLA Academy of Military Sciences/ Walvax Biotech	RNA	Phase I	Phase I trial began end of June 2020	mRNA (ARCoV)

Source: Milken Institute Covid-19 Vaccine and Treatment Tracker

Optimisation programme for Nuvec®

Whilst progressing the COVID-19 project, N4 Pharma continues to conduct studies to further understand the activity of the Nuvec® platform, with the aim to further improve the particle for vaccine delivery. N4 Pharma has outlined an optimisation programme with the work to be completed in two main stages. The first stage of the project is focused on improving the formulation of the Nuvec® particle. The second stage aims to test the improved formulation in cell-based and animal models. This programme should address inconsistencies observed between *in vitro* and *in vivo* studies and generate data that potential partners are likely to request for their evaluation of the platform.

Nanomerics collaboration

The Company has worked with Evotec and the Centre for Process Innovation to optimise the molecule and in January 2020, N4P struck a collaboration agreement with Nanomerics Ltd, a specialist pharmaceutical company focused on pharmaceutical nanotechnology. As part of the collaboration, Nanomerics is developing and evaluating candidate formulations of Nuvec®. The collaboration consists of two stages (outlined below).

1. **Stage 1:** Nanomerics is to develop and test the 30-day stability of four different Nuvec® formulations loaded with a well-known form of pDNA, as well as a novel small interfering RNA (siRNA) molecule. The use of a well-documented form of pDNA aims to enable the comparison of Nuvec® as a vaccine delivery system against existing literature, whilst the siRNA study would indicate the platform's utility as a method to deliver therapeutic siRNA molecules to silence aberrant genes.

2. **Stage 2** aims to test the efficacy of Nuvec® to generate antibodies in an animal model. This would provide further supporting data regarding the ability of Nuvec® to generate an immune response. The stage also includes the option to test the novel siRNA antigen in a gene silencing tumour model. This experiment would demonstrate the utility of Nuvec® as a delivery system for gene therapy.

Nanomerics is based at the University of London, therefore was impacted by the national lockdown restriction due to COVID-19. Prior to the national lockdown, Nanomerics demonstrated that polyethylenimine (PEI) loaded Nuvec® could be dispersed and resuspended in an aqueous solution in preparation for loading of DNA. As of July 2020, Nanomerics was able to resume laboratory work and is now focused on assessing the DNA loading characteristics of the Nuvec® particle.

Nuvec process improvement project plan

Stage	Action
Stage 1	Nuvec® manufacturing process alterations (i.e. addition of PEI onto silica nanoparticles which allows for subsequent loading of DNA/mRNA)
	Nuvec® dispersion testing
	Improved Nuvec® DNA loading process
Stage 2 (Nanomerics collaboration)	Analyse the effect of the Nuvec® concentration, the DNA: Nuvec® ratio and solution composition on DNA: Nuvec® agglomeration
	in vivo testing to measure the antibody response of the improved product loaded with pDNA
	in vitro testing of the improved product loaded with an siRNA antigen (optional)

Source: Company announcements

Nuvec® dispersion project

In vitro studies have indicated that Nuvec® does not produce a monodisperse suspension. Nuvec® particles were observed to agglomerate, i.e. clump together, after DNA was loaded onto the particle. The Group expects that a more monodisperse formulation of Nuvec® would improve transfection efficiency and lead to more consistent results. It could also increase the immune response to a single dose. In January 2020, the Group announced that it had manufactured and tested an improved formulation of Nuvec®. The new formulation was observed to result in a higher level of dispersion than the existing version, prior to the addition of DNA. In November 2020, the Group highlighted it has developed different options to make a fully monodispersed formulation of Nuvec® loaded with pDNA.

Potential to be stored at room temperature

As mentioned, the rollout of nucleic acid-based therapies is hindered by the need to store the vaccine at ultra-low temperatures. Pfizer's mRNA based COVID-19 vaccine requires storage at -70 °C. Initial studies have demonstrated that Nuvec®, loaded with pDNA, can be dried, stored at room temperature and reconstituted without any degradation of the pDNA payload. The formulation is now being stored over different periods of time, after which it will be reconstituted and tested *in vitro* to evaluate if cell transfection (the ability to introduce the pDNA into the target cell) has been maintained. The ability of Nuvec® to be stored at room temperature without affecting its effectiveness would be of significant interest to developers of nucleic acid-based treatments.

Optimisation study to commence in early 2021

An *in vivo* study using Nuvec® generated from the optimisation programme is expected to commence in early 2021. It aims to evaluate the ability of the optimised formulation of Nuvec® to transfect cells and generate antibodies. The study is expected to compare the ability of Nuvec® loaded with the SARS-CoV-2 pDNA and another generic plasmid in generating relevant antibodies. The successful completion of this study would be a significant milestone in the preclinical evaluation of the Nuvec platform. We expect the results to form an important part of the data package for future partnering discussions and guide the protocol for potential first-in-man trials.

Manufacturing scale up of Nuvec®

Currently N4 Pharma and its collaborators can manufacture Nuvec® in the small amounts required for lab-based testing. The Group is now looking to scale-up manufacturing capabilities for Nuvec®. This would provide sufficient resources for later-stage preclinical work and demonstrate to potential partners that Nuvec® can be manufactured at adequate quantities for clinical trials. This work is supported by the proceeds from the May 2020 fundraise. In September, N4 Pharma appointed Ardena, a Dutch-based contract development and manufacturing organisation (CDMO), as its partner for the technology transfer and upscaling manufacture of Nuvec®. The contract consists of three stages:

1. Establishing an understanding of the current manufacturing process for Nuvec®, scale-up and analysis of the transfer of technology;

2. Process optimisation and scale-up resulting in the manufacture and analysis of a non-GMP 50g batch of Nuvec®;

3. Manufacture, testing and product certification of Nuvec® for GMP status.

Ardena has proven experience in the manufacture of nanoparticles, which is of particular relevance for Nuvec®, as it is a silica nanoparticle-based system. This contract should help streamline the manufacturing process for Nuvec® and generate a protocol which can be used to develop a consistent and reliable end-product as well as supporting scale-up and GMP certification. GMP is a quality control system which ensures pharmaceuticals are consistently manufactured to certain standards. Achieving GMP certification would be valuable prior to conducting human trials. We expect the initial stages of the agreement to complete by Q121.

Potential oral application for Nuvec®

As the Company continues to perform studies on Nuvec®, the Directors have become more aware of additional applications of the delivery platform. Whilst N4 Pharma is primarily focused on the development of an injectable vaccine delivery system, the Group recently highlighted the potential to use Nuvec® as an oral vaccine delivery system. This could unlock an additional commercial opportunity for the Group. Oral vaccines may offer advantages over conventional routes of administration, such as injection. The use of oral vaccines is of particular interest in less developed countries, where easier administration and reduced supply chain requirements compensate for a lack of healthcare and logistical infrastructure.

Challenges of oral vaccine delivery

Most vaccines must be kept between 2-8°C from manufacturer to patient

Source: Medicin San Frontieres

Although oral vaccines have multiple potential advantages over conventional methods, there remain challenges in developing vaccines which utilise this administration route. An ideal oral vaccine delivery system would have to safely deliver the antigen through to the intestine, where it can transport across the mucosal barrier and transfect antigen-presenting cells to generate an immune response. There are two key obstacles which any oral vaccine needs to overcome to deliver its payload and generate an adequate immune response. There are certain features of Nuvec® which indicate it could overcome these hurdles:

1) **The harsh environment of the gastrointestinal (GI) tract:** The stomach is a highly acidic environment, whilst the GI tract has a number of enzymes (DNases, Rases, proteases) which can degrade nucleic acid or protein-based antigens. Nuvec® loaded with DNA/RNA is suitable for lyophilisation (freeze drying) and can be loaded onto an acid-resistant capsule. This can protect the particle and vaccine antigens from degradation in the stomach. Furthermore, lyophilisation could enable storage at ambient temperatures. Lipid nanoparticles, another form of vaccine delivery system, are not suitable for lyophilisation and therefore have to be stored at cooler temperatures as a liquid or semi-solid formulation.

2) **The movement and clearance of intestinal matter:** The muscular contractions of the small intestine move matter through the GI tract. If the vaccine is not able to bind to and transfect the mucosal cells lining the epithelium of the intestines it can be expelled without delivering its payload. The spikes on the surface of Nuvec are coated with positively charged PEI. This is expected to support Nuvec's adhesive properties and enable the particle to bind to and subsequently transfect mucosal cells as it passes along the GI tract.

Initial programme for Nuvec® as an oral delivery system

In order to further explore this potential opportunity, N4 Pharma has again partnered with Evotec to undertake preliminary *in vitro* studies to determine the feasibility of using Nuvec® in this area. The Company has acquired gut cells of mice and first aims to see if Nuvec can be optimised to transfect gut cells *in vitro*. If this is successful, the partners would move to similar *in vitro* tests using human gut cells.

The ability of Nuvec® to transfect gut cells is critical in terms of the platforms utility as an oral vaccine delivery system. Therefore, Management are looking to complete these studies prior to progressing the programme further. If these *in vitro* tests are successful, the Group would aim to repeat the testing in animal models and look for the presence of antibody specific responses. Should this project be successful, we expect the Group to undertake further work to ready the programme for first-in-man testing and strike a development agreement to take the project into the clinic with a partner.

Although additional work must be completed to establish the viability of Nuvec as an oral delivery system, the Group highlighted the initial studies are running alongside existing workstreams with no impact on timings and limited additional costs.

Benefits of oral vaccines

Whilst vaccine programmes have been effective public health strategies in reducing diseases, there is scope to increase the effectiveness at a reduced cost. The use of oral vaccines could provide a cost-effect method for vaccination programmes with an increased level of patient compliance. This could increase the effectiveness of vaccination programmes and reduce disease transmission. The rollout of an oral polio vaccine has contributed to the widespread elimination of the polio virus. Commercial benefits of oral delivery include:

- **Easier storage:** Most vaccines need to be stored at a cool temperature as exposure to high temperatures can reduce potency and wasted doses. As a result, vaccines require cold-chain storage from manufacturer to end-user. This can be difficult and expensive, especially in developing regions with tropical climates and a lack of logistical infrastructure. Oral vaccines could be lyophilised (freeze-dried) enabling a longer shelf-life and storage at ambient temperatures.

- **Cheaper to administer:** Most vaccines are administered via injection and require trained medical staff to perform the inoculation as well as disposal of sharps waste materials. Oral vaccines, which can be delivered in tablet formulations, would not require assisted delivery. This should reduce the cost of administration.

- **Increased patient compliance:** Fear of needles can lead to the avoidance of vaccination by a subgroup of the population. This can hinder the effectiveness of vaccination programmes. This would not be an area of concern when using an oral vaccine.

Stimulation of the mucosal immune system

As the GI tract facilitates the passage of foodstuff for digestion, it is constantly exposed to external material including colonies of probiotic bacteria as well as potentially

pathogenic organisms and viruses. As a result, the gut has developed an extensive immune system known as the mucosal system. The mucosal immune response can result in the production of IgA antibodies and the activation of T-cells populations in the intestines. Injection-based vaccines tend to focus only on the systemic immune response, such as the production of IgG and IgM antibodies and cell-mediated immune responses.

Oral vaccines have the potential to activate both the systemic immune response as well as the mucosal response to produce comprehensive protection against a pathogen. As many pathogens enter via the gut, the use of oral vaccines, could prime the mucosal immune response against challenge by a pathogen.

Oral Vaccine developers

Although oral vaccines offer advantages over conventional delivery methods, there are only a few licenced vaccines available. These vaccines primarily consist of attenuated forms of the disease-causing pathogen. FY19 sales for GSK's (GKS.LN) *Rotarix,* a vaccine for rotavirus, were £558m whilst FY19 sales for Merck's (MRK.NY) *RotaTeq* were US$791m (FY18: US$728m). Valneva (VLA.EPA) is selling Dukoral, an oral vaccine for traveller's diarrhoea with FY19 sales of EUR31.5m.

There are multiple oral vaccines in clinical development, including for COVID-19. Vaxart (VXRT.NQ) is developing an oral adenovirus-based COVID-19 vaccine. The group recently released preclinical animal data which suggested that the vaccine candidate can induce both a humoral and cellular immune response in the serum and mucosal system. The group's candidate recently entered Phase 1 clinical trials. Vaxart previously received $15.7m from BARDA to support the development of oral influenza vaccines.

Merck (MRK.NY) and the International AIDS Vaccine Initiative, IAVI, an NGO, are collaborating on the development of V590, an oral COVID-19 vaccine candidate. V590 uses an attenuated strain of vesicular stomatitis virus, a common animal virus that has been modified to express proteins that stimulate an immune response. The candidate is expected to enter human trials by the end of the year. UK-based Stabilitech (Private) is developing OraPro-COVID-19™, another viral vector based oral vaccine candidate with the aim to enter clinical trials for COVID-19 this year. Canadian Symvivo (Private) are using a live cell probiotic-based gene delivery platform to deliver pDNA encoding the SARS-CoV-2 Spike protein to the gut to generate an immune response.

Licensed oral vaccines

Oral vaccine	Disease	Manufacturer
Vivotif	Typhoid fever	Paxvax
Dukoral	Cholera	Valneva
Envichol		Eubiologics
Cholvax		Incepta
Shanchol		Sanofi
Biopolio B1/3	Polio	Bharat Biotech
RotaTeq	Rotavirus	Merck
Rotarix		GSK

Source: Biomedical Journal of Scientific & Technical Research (BJSTR)

Launch of Nuvec® Oncology Treatment Programme

In November, N4 Pharma outlined a new programme to test the use of Nuvec® for the delivery of oncology therapies. The project aims to evaluate the use of Nuvec® as a delivery system for nucleic acid-based therapies with anticancer potential. The Group has appointed Nanomerics, who are currently conducting the optimisation programme, to complete a preclinical proof of concept study. The study consist of two parts:

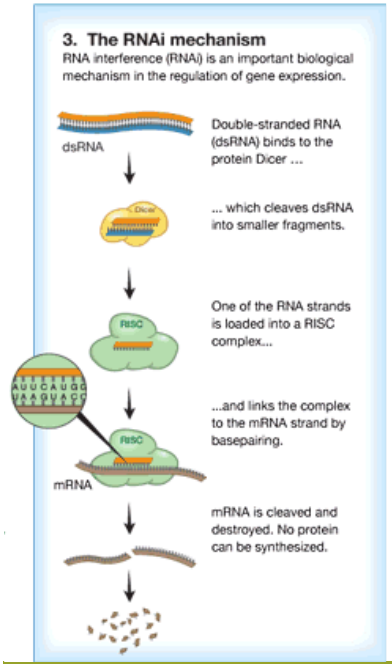
1. The first stage of the programme is focused on developing a formulation of Nuvec® with a therapeutic DNA plasmid.

2. The second stage of the programme aims to evaluate a candidate formulation of Nuvec® *in vivo* in a subcutaneous tumour model to examine tumour regression following multiple local or systemic injections.

The programme is expected to commence imminently and is expected to take up to twelve months. The Group highlighted that the structure of the Nuvec® particle could enable testing as a combination therapy. Whilst the nucleic acid payload could be carried on the surface of the particle, a small molecule chemotherapy could be carried in the hollow core. This dual mechanism could increase the ability to reduce tumour progression. Should the evaluation be a success it could unlock an additional commercial opportunity for the Nuvec® platform.

The use of gene silencing could be used to prevent the translation of genes that have become hyperactive through cancer. The technique relies on the delivery of double stranded RNA, known as short interfering RNA (siRNAs) into the target cell. The siRNAs prompt the cellular machinery to cleave any mRNA molecules present which carry the same genetic code as the siRNA, thus silencing the gene. Therapies which utilise gene silencing are a relatively new class of treatment. In 2018, the FDA approved Alnylam's Onpattro for the treatment of a rare disease. This was thought to be the first siRNA treatment approved in the US.

Mechanism of RNAi



Source: NobelPrize.org. Nobel Media AB (2018).

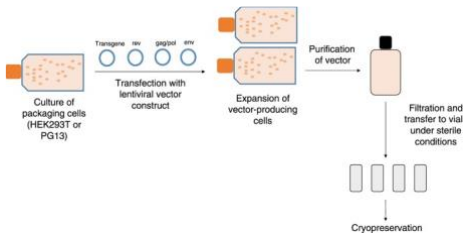
Growing interest in the use of RNAi against cancer

Although the development of new targeted treatments, such as checkpoint inhibitors, have brought an improvement in survival rates, cancer remains a global health challenge. Whilst the pandemic has driven the use of nucleic-based therapies against infectious diseases, the application of the technology in other areas, such as cancer is of growing interest. Treatments such as chemotherapy, radiation and surgery are commonly used to treat cancer however can lead to damaging side effects. The use of RNAi could provide a targeted method to silence the aberrant gene expression which may be contributing to cancer formation. There are multiple companies developing RNAi based treatments for cancer. Sirnaomics Inc. (private) is developing STP705, an RNAi therapy, which silences expression of two genes, TGF-β1 and COX-2 gene expression. The group recently completed an open-label phase 2a trial for STP705 in a form of skin cancer and subsequently closed a US$105m Series D financing round. Similarly to DNA/RNA vaccines, most siRNA therapies use a lipid-based delivery system. Nuvec® could offer an alternative platform to current delivery methods with additional benefits, such as a higher safety profile and increased protection of the payload from degradation.

Use of Nuvec® in viral vector manufacture

Whilst the Company is focused on the use of Nuvec® as a therapeutics delivery system, the Group has outlined an opportunity to use the platform to support viral vector manufacturing. Viral vectors are modified viruses which are used to deliver desired genetic material into a target cell. The global viral vector manufacturing industry is estimated to grow at a CAGR of 22.1% to reach a market size of US$1.5b in 2025 from US$443.6m in 2019. (ResearchAndMarkets.com).

Lentiviral delivery process



Source: MSF

In 2020, the Group demonstrated that Nuvec® can be loaded with the three pDNA plasmids required for the transfection and production of lentivirus, a common viral vector system. Subsequently, the Group performed *in vitro* studies demonstrating that 5µg of triple plasmid loaded onto Nuvec could transfect cells and generate lentivirus and in April 2020, filed a new UK patent application around the use of Nuvec® as a method for viral vector manufacturing.

In their latest financial results, the Company highlighted that it remains focused on progressing other opportunities, such as the oral vaccine programme. However, the use of Nuvec® to manufacture of viral vectors remains a viable market opportunity in the future.

Intellectual Property

N4 Pharma is looking to build a robust IP estate surrounding the use of Nuvec® to protect the use of the platform and support discussions with potential partners. In January 2016, N4P struck a commercial agreement with the University of Queensland for the exclusive rights for Nuvec® for DNA and mRNA delivery. Once N4 Pharma has established the relevant commercial potential it can, at any time, sign a licence for these patent applications with the university.

Nuvec® is licensed by the Company from the University of Queensland under their silica nanoparticle patent application, the core patent for Nuvec. This patent is currently under review by a number of patent offices. If granted, the patent is expected to provide protection regarding the use of Nuvec® up to April 2036. Dialogue remains ongoing but the application has received responses from all the key patent examiners.

N4 Pharma continues to file patents regarding Nuvec® to protect additional market opportunities. In 2018, the Group filed a Patent Cooperation Treaty (PCT) patent application covering on improvements made to the manufacturing process of Nuvec® and how the platform can be used to improve delivery of nucleic acids. If granted, the patent should provide an extra 30 months protection for Nuvec® after expiry of the in licensed IP which is likely to expire in April 2036. In April 2020, the Group filed a UK patent application regarding the use of Nuvec® to support the manufacture of viral vectors in applications such as ex-vivo gene therapy treatments.

Vaccine market overview

The vaccine market has historically been dominated by four large pharma companies, (GSK, Sanofi, Merck and Pfizer). Conventional vaccines use an inactivated or weakened (attenuated) versions of the pathogen or a protein taken from the pathogen. S&P estimated that the global market for vaccines in 2019 generated $33b in revenue which is forecast to grow by 5-7% over the next five years. This does not include potential revenues from a COVID-19 vaccine, which is expected to significantly increase the market size. The pandemic has expedited the development of novel approaches including nucleic acid-based vaccines. As a delivery system for nucleic acids, this should have a positive read across for Nuvec®.

Growing pipeline of DNA/RNA based vaccines

Companies such as Moderna and BioNTech have RNA-based COVID-19 vaccine candidates in late-stage clinical trials. Although there has not been an approved nucleic acid-based vaccine to date, the successful completion and roll-out of a DNA/RNA based COVID-19 vaccine would generate clinical acceptance of the technology and accelerate market growth. According to ClinicalTrials.gov, there are currently 129 DNA vaccine trials and 323 RNA vaccine trials ongoing. This highlights the growing pipeline of nucleic acid-based vaccines in future medical approaches.

Advantages of nucleic acid vaccines

Whilst conventional vaccine approaches have supported the elimination of life-threatening diseases in many countries, new technologies, such as DNA/RNA based vaccines may offer additional advantages. In terms of safety, the use of live-attenuated vaccines has a small risk of the vaccine virus reactivating, which can lead to disease. This occurred with a polio vaccine, leading to vaccine-derived poliovirus in a small portion of patients. As nucleic acid vaccines only encode for a portion of the pathogen there is little risk of this occurring.

Faster manufacturing scale up

An important feature for effective vaccine programmes is the ability to develop, test the candidate and scale up manufacturing of the vaccine. Live-attenuated, inactive and subunit vaccines typically use a cell-based manufacturing process. Not only is this a relatively slow process, a new manufacturing procedure is required if a change in antigen target is required. This could increase the time to deployment if the pathogen mutates. RNA/DNA molecules can be rapidly generated using high yielding *in vitro* assays. Furthermore, if the pathogen mutates, the sequence of RNA/DNA can be easily modified with little impact on downstream manufacturing processes. This can result in a shorter time to deployment, as demonstrated by Moderna's RNA-based vaccine candidate being the first COVID-19 vaccine to enter the clinic.

Potential improved safety profile

An alternative vaccine approach is the use of viral-based vectors to deliver an antigen. These use a harmless viral vector, such as adenovirus, which is genetically modified to express an antigen from the target pathogen. An issue for this delivery system is the pre-existing neutralising antibodies against the adenovirus viral vector. This could lead to the degradation of the vaccine prior to generating an immune response. Some developers use non-human adenovirus, such as AstraZeneca's (AZN.L) COVID-19 vaccine candidate, AZD1222, which utilises a chimpanzee adenovirus vector. However, there still may be cross-reactivity in the immune system for these vectors, and the immune system may adapt to the vector which could impact the effectiveness of repeat dosing. As DNA/RNA vaccines do not use a viral vector they are not exposed to this issue. Furthermore, both Johnson & Johnson (JNJ.NY) and AstraZeneca (AZN.L) had to temporarily pause dosing in Phase 3 clinical trials testing their viral-vector based COVID-19 vaccine candidates due to unexplained illness observed in patients. Both AZD1222 and JNJ-78436735 use an adenoviral vector platform and, given the intense scrutiny of COVID-19 vaccine trials, this has raised safety questions surrounding the technology.

Comparison of different vaccine systems

Type of vaccine	Method of action	Advantages	Disadvantages	COVID-19 candidates
DNA vaccine	Deliver DNA to cells to generate protein antigens to stimulate immune system	Non-infectious; egg and cell free manufacturing; rapid scalable manufacturing process which can be easily modified for new target antigen	Potential integration into human genome; No licensed version	Inovio
RNA vaccine	Deliver RNA to cell which is translated to protein antigen to stimulate immune system	Non-infectious; Non integrating; egg and cell free manufacturing; rapid scalable manufacturing process which can be easily modified for new target antigen	Potential instability and low immunogenicity; No licensed version	Moderna; BioNTech
Viral vector	Deliver virus genetically modified to express antigen of pathogen of interest to stimulate immune system	No adjuvant; potent immune response	Cell-based manufacturing; Pre-existing immunity against viral vector; potential risk of inflammation	AstraZeneca; Johnson & Johnson
Live attenuated or inactivated	Weak or inactive version of pathogen of interest	Potent immune response; no adjuvant required; history of approved use	Cell-based manufacturing; new manufacturing line required for new antigen target; Risk of reversion in attenuated vaccines	
Subunit	Deliver portion of pathogen of interest which stimulates immune system	Non-infectious; strong antibody response; history of approved use	Cell-based manufacturing; new manufacturing line required for new antigen target; adjuvant required	Novovax

Source: CDC; NIAID; Company websites

Current nucleic acid vaccine delivery systems are sub-optimal

Despite the growing interest in the use of nucleic acid vaccines, current delivery systems remain sub-optimal for widespread use. The use of lipid nanoparticles remains one of the most popular methods of nucleic acid delivery. However, the technology has potential issues such as liver-toxicity and a short shelf-life. The use of electroporation or an air jet injection are other DNA delivery routes however, these are expensive techniques which require novel medical devices and can cause side effects. The use of Nuvec® can an alternative delivery system which can overcome the disadvantages observed in other techniques. We expect the technology to be of significant interest to DNA/RNA vaccine developers who are looking to optimise their assets.

Comparison of DNA delivery systems

Delivery system	Method of action	Advantages	Disadvantages	Developers
Electroporation	Electric pulse to form pores in cell membrane to transfer DNA	Rapid, effective transfection	Expensive, excess cell death due to high voltage	Inovio
Jet injection	High velocity expulsion of DNA into skin tissue	Low volume of DNA required, strong humoral response	Power of expulsion can damage DNA payload and patient tissue	Takara Bio; DIOSynVax
Lipid nanoparticle	DNA payload encapsulated by phospholipid membrane	Easily synthesised, protect against degradation, scalable	Cellular toxicity and accumulation in liver leading to hepato-toxicity; short shelf-life	Moderna; BioNTech
Silica nanoparticle	DNA payload bound to silica-based particle	High capacity loading, protect against degradation,	No long-term safety data	N4 Pharma

Source: Company reports

Financials

Income statement

Fiscal Year Fiscal period end-date £	2017A 31/12/2017	2018A 31/12/2018	2019A 31/12/2019	H120A 30/06/2020
Government Grant Income	109,913	72,832	-	-
Total revenue	**109,913**	**72,832**	**-**	**-**
Costs of goods sold	-	-	-	-
Gross profit	**109,913**	**72,832**	**-**	**-**
R&D expenses	(409,808)	(846,176)	(216,948)	(213,869)
General & Admin. (incl exceptionals)	(316,632)	(643,745)	(730,392)	(371,197)
Reorganisation costs	(281,298)	-	-	-
Depreciation & Amortisation	-	-	-	-
Total overhead expense	**(1,007,738)**	**(1,489,921)**	**(947,340)**	**(585,066)**
Operating profit	**(897,825)**	**(1,417,089)**	**(947,340)**	**(585,066)**
Finance income/(expenditure)	(5,299)	(981)	(1,385)	21
Acquisiton cost	(1,023,734)	-	-	-
Gain on sale of investment	-	27,693	-	-
Profit before tax	**(1,926,858)**	**(1,390,377)**	**(948,725)**	**(585,045)**
Tax	89,874	205,534	72,352	46,657
Profit after tax	**(1,836,984)**	**(1,184,843)**	**(876,373)**	**(538,388)**
Ordinary Shares in issue (Basic)	64,783,082	89,440,373	100,168,016	113,169,749
Ordinary Shares in issue (Diluted)	27,852,274	91,305,287	100,168,016	114,298,028
Basic EPS (GBp)	**(1.26)**	**(1.32)**	**(0.87)**	**(0.48)**
Diluted EPS (GBp)	**(1.24)**	**(1.30)**	**(0.87)**	**(0.47)**

Source: Company reports; SP Angel forecasts

SP Angel | Prince Frederick House | 35-39 Maddox Street | London | W1S 2PP | United Kingdom

Cash Flow

Fiscal Year Fiscal period end-date £	2017A 31/12/2017	2018A 31/12/2018	2019A 31/12/2019	H120A 30/06/2020
Profit/(Loss) before tax	**(1,926,858)**	**(1,390,377)**	**(948,725)**	**(585,045)**
Finance expenditure	5,299	981	1,385	(21)
Deemed cost of acquisition	1,023,734	-	-	-
Share based payments to employees	-	629	3,767	(1,538)
Gain on sale of investments	-	(27,693)	-	-
Operating gain/(loss) before changes in working capital	**(897,825)**	**(1,416,460)**	**(943,573)**	**(586,604)**
Movements in working capital				
Trade and other receivables	(109,513)	(9,266)	29,441	39,210
Trade and other payables	56,538	10,905	(112,440)	70,987
Taxations	-	70,574	220,568	46,657
Cash used in operations	**(950,800)**	**(1,344,247)**	**(806,004)**	**(429,750)**
Net cash flows used in operating activities	**(950,800)**	**(1,344,247)**	**(806,004)**	**(429,750)**
Investing activities				
Cash acquired on reverse acquisition	402,990	-	-	-
Sale of investments	-	27,693	-	-
Net cash flows from investing activities	**402,990**	**27,693**	**-**	**-**
Financing activities				
Finance expenditure	(5,299)	(981)	(1,385)	21
Net proceeds of ordinary share issue	1,988,970	784,404	980,000	1,907,495
Cost of share issue	(129,340)	-	-	
Net cash flow from financing activities	**1,854,331**	**783,423**	**978,615**	**1,907,516**
Net increase/(decrease) in cash and cash equivalents	1,306,521	(533,131)	172,611	1,477,766
Cash and cash equivalents at the beginning of the period	19,751	1,326,272	793,141	965,752
Cash and cash equivalents at the end of the period	**1,326,272**	**793,141**	**965,752**	**2,443,518**

Source: Company reports; SP Angel forecasts

SP Angel | Prince Frederick House | 35-39 Maddox Street | London | W1S 2PP | United Kingdom

Balance sheet

Fiscal Year Fiscal period end-date £	2017A 31/12/2017	2018A 31/12/2018	2019A 31/12/2019	H120A 30/06/2020
Investments	-	-	-	-
Property, plant & equipment	-	-	-	-
Intangible assets	-	-	-	-
Receivables	-	-	-	-
Total non-current assets	**-**	**-**	**-**	**-**
Trade and other receivables	132,700	276,926	99,269	60,059
Cash and cash equivalents	1,326,272	793,141	965,752	2,443,518
Total current assets	**1,458,972**	**1,070,067**	**1,065,021**	**2,503,577**
TOTAL ASSETS	**1,458,972**	**1,070,067**	**1,065,021**	**2,503,577**
Trade and other payables	(143,788)	(159,666)	(51,547)	(127,837)
Accruals and deferred income	(35,430)	(30,457)	(26,136)	(20,833)
Borrowings and loans	-	-	-	-
Total current liabilities	**(179,218)**	**(190,123)**	**(77,683)**	**(148,670)**
Total non-current liabilities	**-**	**-**	**-**	**-**
TOTAL LIABILITIES	**(179,218)**	**(190,123)**	**(77,683)**	**(148,670)**
Share capital	8,579,396	8,634,675	8,676,675	10,705,925
Share premium	8,513,670	9,328,848	10,327,258	10,181,317
Share option reserve	147,635	81,909	25,266	47,914
Reverse acquisition reserve	(14,138,244)	(14,138,244)	(14,138,244)	(14,138,244)
Merger Reserve	299,045	279,347	279,347	279,347
Retained Earnings	(2,121,748)	(3,306,591)	(4,182,964)	(4,721,352)
TOTAL EQUITY	**1,279,754**	**879,944**	**987,338**	**2,354,907**

Source: Company reports; SP Angel forecasts

Key Risks

N4 Pharma is an early stage healthcare company and is exposed to risks inherent to both the sector. Of the risks outlined below development and regulatory risk are the most relevant to the Company.

Development risk

As a preclinical company N4 Pharma has not yet generated human data using its product candidates. Preclinical testing can be lengthy and uncertain with no guarantee N4 Pharma will receive approval to test their products in humans. There is no guarantee that results in preclinical tests will be replicated in humans. Positive results from early stage clinical studies performed by the Company or by a third party for product development may not necessarily be predictive of the results of later stage studies.

Operational Risk

The Group is at an early stage of development with no guarantee of future revenues. The group has a limited operating history upon which its performance and prospects can be evaluated and faces the risks frequently encountered by developing companies.

Regulatory Risk

There is no guarantee that N4 Pharma will receive marketing approval for one or more of Nuvec's product lines. A delay or failure to receive marketing approval could have negative impact on the Company's operation. There is no guarantee that any product will be able to achieve the necessary regulatory approvals. Any changes may have an adverse effect on the Group's operations.

Trial Risk

The outcome of clinical trials cannot be pre-determined with no guarantee of future clinical trials conducted by N4 Pharma meeting a primary end point. The Company's development programs are always at risk of termination should a future trial raise concerns about a products safety or efficacy. There may requests for additional clinical data which would require additional working capital. Enrolment delays may result in increased development costs and delays in licensing, marketing and commercial launch.

Key Personnel

The loss of key management personnel would have a negative impact on the Company's strategy and ability to achieve future milestones.

Protection of intellectual property

The Group's ability to compete significantly relies upon successful protection of its intellectual property, in particularly its licensed and owned patent applications for Nuvec. The Group seeks to protect its intellectual property through the filing of worldwide patent applications and confidentiality obligations for its employees. This however does not guarantee that a third party will not infringe on the Group's intellectual property, release confidential information about the intellectual property of claim technology registered to the Group.

Key Management

Nigel Theobald: Chief Executive Officer

Nigel has over 25 years' experience in healthcare and in building businesses, strategy development and its implementation and a strong network covering all aspects of pharmaceutical product development and commercialisation. He was the head of healthcare brands at Boots Group plc in 2002 before leaving to set up a series of successful businesses, including Oxford Pharmascience Group plc, which he grew over 5 years into an AIM quoted company with a market capitalisation of £40 million upon departure. Nigel formed N4 Pharma in 2014.

Dr John Chiplin: Non-Executive Chairman

Dr Chiplin has significant operational, investment and transaction experience in the life science and technology industries. Between 1995 and 2014, Dr Chiplin served as CEO of three leading publicly listed software, biotechnology and cancer immunotherapy companies in the US. Based in London, Dr Chiplin's current board roles include Adalta, Cynata, Regeneus and Scancell Holdings plc (AIM: SCLP). He is also Managing Director of Newstar Ventures Ltd, an international PE firm focused on emerging companies.

Dr David Templeton: Technical Director

An experienced R&D manager who has worked in major pharmaceutical, biotech and in the generic industry with specific expertise in early clinical development and translational biology, toxicology and safety pharmacology, lead selection, candidate characterisation, PK/PD analysis and bioanalysis. David has worked in various pharmacology and preclinical drug discovery roles for Pfizer, Xenova, Smithkline Beecham and GSK and was the head of non-clinical development at Celltech Limited from 2003 to 2004 before moving to Merck Generics UK as head of biometrics. He was appointed as director of clinical pharmacology of Eisai Limited in 2007 until in 2010 setting up his own consulting business offering discovery and early development advice to several pharmaceutical companies.

Luke Cairns: Executive Director

Luke has spent over 20 years working in corporate finance and is a former head of corporate finance and managing director at Northland Capital Partners, an FCA regulated stockbroking firm. Having left Northland in 2014, Luke founded LSC Advisory Limited to provide advisory and consultancy services to growth companies. He has worked with many growth companies across a number of sectors and regions on a wide range of transactions, including IPOs, secondary fundraisings, corporate restructurings and takeovers. He is an Associate of the Chartered Institute of Secretaries.

Dr Chris Britten: Non-Executive Director

Experienced pharmaceutical executive who is currently Head of M&A at Neuraxpharm, a privately-owned European CNS specialty pharmaceutical company. He has over 20 years' experience in R&D, corporate development and investment banking. Previous roles include Global Head of M&A at Sandoz (Munich), Managing Director at Torreya Partners (London), Head of Business Development at Sanofi Pasteur MSD (Lyon) and Director, Life Sciences at Deloitte Corporate Finance (London). Chris also spent many years at GSK in both drug discovery and corporate development.

Disclaimers

This note has been issued by SP Angel Corporate Finance LLP ("SP Angel") in order to promote its investment services and is a marketing communication for the purposes of the European Markets in Financial Instruments Directive (MiFID) and FCA's Rules. It has not been prepared in accordance with the legal requirements designed to promote the independence or objectivity of investment research and is not subject to any prohibition on dealing ahead of its dissemination.

SP Angel considers this note to be an acceptable minor non-monetary benefit as defined by the FCA which may be received without charge. In summary, this is because the content is either considered to be commissioned by SP Angel's clients as part our advisory services to them or is short-term market commentary. Commissioned research may from time to time include thematic and macro pieces. For further information on this and other important disclosures please the Legal and Regulatory Notices section of our website Legal and Regulatory Notices

While prepared in good faith and based upon sources believed to be reliable SP Angel does not make any guarantee, representation or warranty, (either express or implied), as to the factual accuracy, completeness, or sufficiency of information contained herein.

The value of investments referenced herein may go up or down and past performance is not necessarily a guide to future performance. Where investment is made in currencies other than the base currency of the investment, movements in exchange rates will have an effect on the value, either favourable or unfavourable. Securities issued in emerging markets are typically subject to greater volatility and risk of loss.

The investments discussed in this note may not be suitable for all investors and the note does not take into account the investment objectives and policies, financial position or portfolio composition of any recipient. Investors must make their own investment decisions based upon their own financial objectives, resources and appetite for risk.

This note is confidential and is being supplied to you solely for your information. It may not be reproduced, redistributed or passed on, directly or indirectly, to any other person or published in whole or in part, for any purpose. If this note has been sent to you by a party other than SPA the original contents may have been altered or comments may have been added. SP Angel is not responsible for any such amendments.

Neither the information nor the opinions expressed herein constitute, or are to be construed as, an offer or invitation or other solicitation or recommendation to buy or sell investments. Opinions and estimates included in this note are subject to change without notice. This information is for the sole use of Eligible Counterparties and Professional Customers and is not intended for Retail Clients, as defined by the rules of the Financial Conduct Authority ("FCA").

Publication of this note does not imply future production of notes covering the same issuer(s) or subject matter.

SP Angel, its partners, officers and or employees may own or have positions in any investment(s) mentioned herein or related thereto and may, from time to time add to, or dispose of, any such investment(s).

SPA has put in place a number of measures to avoid or manage conflicts of interest with regard to the preparation and distribution of research. These include (i) physical, virtual and procedural information barriers (ii) a prohibition on personal account dealing by analysts and (iii) measures to ensure that recipients and persons wishing to access the research receive/are able to access the research at the same time.

SP Angel Corporate Finance LLP is a company registered in England and Wales with company number OC317049 and whose registered office address is Prince Frederick House, 35-39 Maddox Street, London W1S 2PP. SP Angel Corporate Finance LLP is authorised and regulated by the Financial Conduct Authority whose address is 12 Endeavour Square, London E20 1JN.

Recommendations are based on a 12-month time horizon as follows:

Buy - Expected return >15%

Hold - Expected return range -15% to +15%

Sell - Expected return < 15%