

Category

Best Startup

Product/Solution Name

NeuroMotor Pen™

Date of Approval

N/A

Indications

Prevention screening: Detection of early stage/subtle movement abnormalities and differentiating benign movement abnormalities (such as benign tremors) from Parkinson's disease. This enables the large number of patients (>10 million) with benign movement/tremor problems to be reassured whilst those with suspected Parkinson's can be triaged to the right specialist for a timely diagnosis.

Differentiating tremors from Parkinson's disease for use in primary care

Aid to diagnosis in specialist care for 'difficult' to diagnose Parkinson's disease

Objective and accurate monitoring movement symptoms in Parkinson's disease with novel digital biomarkers, based on fine motor skill assessment enabling higher granularity and accuracy measurements than wearables or smartphones or (subjective) clinical rating scales.

Detection of neurotoxicity - an adverse effects of CAR T-Cell immunotherapy for treatment of a various types of cancer. Early detection of neurotoxicity can avoid progression of neurotoxicity from grade 1 to grade 4 that leads to irreversible neurological problem and which can be lethal.

Therapeutic Categories

Motor symptoms monitoring in Parkinson's with clinical outcome assessment for drug treatment

Tremor symptoms monitoring in tremor disorders (other than Parkinson's), such as essential tremor with clinical outcome assessment for drug treatment and device treatment, e.g. with nerve stimulation devices

Neurotoxicity detection in CAR T-Cell therapy

Attached Files:

- ManusNeuro NMP introduction brochure 4ppv2 3.pdf

Background information and need for solution/product

The NeuroMotor Pen™ (NMP) platform is a unique scalable digital solution for detection and quantification of movement and cognitive symptoms, using novel sensor technologies built into a digital pen with an analytical engine with AI Decision Support. The interface enables recording 50 'digital biomarkers' that provide objective and quantitative information about movement

abnormalities. An AI algorithmic overlay enables the accurate differentiation between movement disorders. Designated as “Breakthrough Device” by FDA, NMP is the only device with clinical claims for differential diagnostic decision making in Tremor. Its initial application will be in differential diagnosis and monitoring of essential tremor and Parkinson’s – a \$1 billion recurring income opportunity in US.

NMP portability enables neuro disease & drug adverse effects assessment to be delivered in low-cost channels, e.g. pharmacies, urgent care clinics & at home. The NMP (pen + tablet + AI) enables to build a new line-of-business, providing neurological disease management as an entry-level service.

Over time the NMP platform tech will be extended into Alzheimer’s Disease (AD) and schizophrenia and a broad range of other neurological diseases. R&D with clinical studies are already ongoing for AD and schizophrenia. In addition, Manus and J&J have signed an agreement and are implementing a clinical trial with Manus to validate the potential for NMP to support administering CAR T-cell immunotherapies in a safer way by detecting adverse effects that otherwise lead to irreversible neurotoxicity and sometime death. Through telemonitoring, patients will no longer have to stay in hospitals for several weeks following immunotherapy, therefore avoiding 30% of additional immunotherapy treatment expenditure. Ongoing discussions with J&J and virtual ward providers are aimed at creating a consortium to roll out the solution.

Manus was founded with the intention to deliver the NMP as a platform technology for non-invasive and low-cost digital neuro assessments that can be made available anywhere needed. This was a response to the need for improved neuro assessments in an aging society, where neurological disorders are on the rise and are the leading cause of disability [1]. Currently, as many as 100 million American already suffer from one or more neurological disorder [2] and cope with movement and/or cognitive impairments. Parkinson’s (PD) is the fastest growing disorder [3]. By 2037, there will be an increase from currently 1 million to 1.6 million patients with PD with a cost burden of 79 billion [4]. However, the bigger problem is that there are more than 10 million people with movement problems, including tremor, who are concerned about the nature of symptoms and worry that they may develop Parkinson’s. Given that primary care is does not diagnose or treat neurological disorders and is often insufficiently equipped to provide reassurance to those with benign movement disorders, specialist clinics are often overburdened and struggle to make a timely diagnose and provide personalized treatments with regular follow up. A more patient centred approach is needed [5].

In addition, even for specialists, making differential diagnostic decisions is difficult. A clinical diagnosis is mainly based on clinical symptoms with as only tools clinical rating scales (observation) and sometime brain scans, but these are expensive and uncomfortable for patients and not conclusive. Digital health solutions are currently non-existent in neurology settings.

Crucially important for differential diagnostic decision-making is NMP’s tremor assessment information. Tremor is the major symptom for 90% of Parkinson’s sufferers [6, 7, 8] and tremor is an extremely complex feature in Parkinsonism. Differentiating between a Parkinsonian tremor and other tremor disorders is challenging even for experienced neurologists [9] and the separation of PD from Essential Tremor (ET) accounts for about half of the misdiagnoses [10]. The lack of tremor measurement equipment in the clinic and not being able to identify subtle tremors is part of the cause for not being able to differentiate between PD and ET. Moreover, subtle tremors, are often already present in the prodromal stage before a clinical diagnosis can be made [11]. A major breakthrough in establishing an early diagnosis lies in measuring and quantifying the earliest changes in the neuromuscular system, and in particular tremor, due to Parkinsonism [12, 13, 14, 15]. The

NeuroMotor Pen delivers this breakthrough. Please see details in the following appendix: Manus NMP white paper – improving the standards of care diagnostic accuracy with NMP as aid.

Manus' proposition is to streamline the patient pathway with the NeuroMotor Pen™, enabling both primary care and pharmacy retail outlet to implement prevention screening and reassure those with benign movement problems while triaging those who need to be seen by specialists. This creates a new line of business in low-cost retail settings for out of pocket pay that provides reassurance for the majority of patients.

Manus has signed up a well-established prevention screening partner – Medispa - in Italy, who has integrated NMP into its 'prevention suite' and is rolling NMP out into pharmacy retail and large corporates for patient screening through HR departments (as well as screening for pharmaceutical trial recruitment). Initial success in Europe is already leading to positive discussions with US-based community based health screening providers about implementing a sustainable, scalable and profitable model that will positively impact those suffering from neurological disorders.

In addition, in specialist settings, NMP is used as 'aid to differential diagnosis', where it was proven to enable making a faster diagnosis. Clinical studies in the UK's National Health Service demonstrated that the clinical diagnostic accuracy improved from 38-65% (which is regarded as typical in the current standards of care with reference measure neuropathologic findings) [16, 17] to 80% at the first specialist appointment with NMP [18]. This is a significant improvement over the standard of care as it typically takes 6-24 months and sometimes longer to confirm the clinical diagnosis. Reaching 80% accuracy at the first appointment reduces the need for multiple appointments over a 6-24 month period to clinically confirm Parkinson's, reducing expenditure on appointments and approximately half of the brain scans.

The Manus NMP tech combined with pharmacy infrastructure will be disruptive. NMP with digital data that can be shared becomes an enabler and connector for all other players in the patient journey: charities, pharmaceutical companies, pharmacies and clinicians involved with diagnosis and treatment.

The pharmacists are trusted by both patients and clinicians, enabling to engage clients in prevention screening (shown in the contract with Medispa, Italy) to then perform patient assessments in a very efficient way to support diagnostic and monitoring of drug treatment by clinicians. Notably, pharmacies and clinicians are already working more and more closely together. An example is MD village being acquired by Walgreens to increase their clinical footprint. NMP will facilitate this and streamline the patient journey.

To conclude, NMP has the potential to support early detection, reaching a faster diagnosis (reducing the time and number of assessments required to establish a clinical diagnosis) and improve monitoring and treatment optimisation for progressive neurological disorder(s). The ultimate aims are streamlining patient pathways, creating patient health benefits & reducing anxiety of patients/carers /family, while enabling time reduction and enormous cost savings for healthcare providers.

Attached Files:

- Manus NMP White Paper improving Standard of Care diagnostic accuracy with NMP as aid Prix Galien US submission final.pdf

History of the development of the solution/product

The NMP product and clinical claims are based on sound scientific work along with deep understanding of the market with standard of care. Prior scientific research in neuroscience planted a seed in the head of the founder for the development of the NMP concept. Prior to Company inception, market analysis confirmed the need and precise utility with clinical claims and device requirements. At the inception, £180,000 was raised for the initial proof of concept R&D project, which was successfully completed and the NMP concept patented. The European Commission (EC) awarded €1.8 million of grant funding (under grant agreement 262291) to collaborate with world class R&D performers in the DiPAR project to progress R&D towards product development with clinical validation studies.

Manus laid out the DiPAR project plan and scientific contents and developed the bid to the EC and assembled the project consortium. The consortium included: the University Medical Centre Groningen (Netherlands) with key opinion leaders in neurology Prof Nico Leenders and Dr Teus van Laar; the expert team in signal processing and AI for digital health solutions at the technical research center of Finland, led by Prof Mark van Gils; experts in sensor and software development with Fraunhofer institute IPA Munich and IPMS Dresden and data science group at Glasgow University, who implemented novel secure data transport and storage facilities. In addition, two Germany SMEs and a Spanish SME developed product components. Manus' founding CEO took responsibility for project coordination, including consortium management and financial management with audited accounts for the project and reporting to the EC as well as technical project management and integration.

The goal of the DiPAR project was to develop the innovative NMP tech from the ground up and fit for purpose. There was no other aid for differential diagnosis of movement disorders on the market. Claims were defined, including use as 1) 'aid to diagnosis' of PD and 2) longitudinal objective monitoring of movement symptoms with automated record keeping alongside/instead of the subjective UPDRS rating scales. Project outputs included: a) the NMP digital stylus with a unique sensor system for quantification of fine motor skill and movement symptoms, b) standardized clinical NMP tasks that bring out the movement abnormalities and c) analytical engine to extract the digital biomarkers that represent movement problems along with AI for decision support. Additionally, e) the go to market strategy with continued productization was delivered by Manus.

The DiPAR project was successfully completed after 4 years and resulted in a clinically validated pre-production prototype with claims for differential diagnostic and monitoring use that were published in peer reviewed journals, reporting on:

- NMP standardised drawing tasks for assessment [19,20,21,22,23];
- Accurate quantification of symptoms and rating medication effects, similar to the Purdue pegboard task (reference measure) [19, 21].
- NMP scores match standard Unified Parkinson's Disease Rating Scale [19,21].
- High reproducibility [20].
- Accuracy > 80% differential diagnosis of Parkinson's vs other; sensitivity 86% [22,23].
- Usability: Automated record keeping; Can be used at home by non-experts [21,23]

The project featured on Euronews and in the EC's promotional videos and was shortlisted in 2022 for the EU impact price in 2022.

Following DiPAR, Manus progressed productization and the following milestones were achieved:

- Successful product development, following prototype development. During this time Manus forged a collaboration with Schwann-Stabilo for co-development of the NMP stylus. An exclusive manufacturing

and supply agreement with quality agreement is in place with Stabilo.

- Further successful EU clinical trials. A peer reviewed journal publication is being prepared with Prof Richard Walker (UK) and PD Dr Angela Deutschlander (Germany and US).
- A study of 150 patients in the Northumbria NHS Trust' (Prof R Walker), evaluated User acceptance of the NMP system and its graphical task regimen in clinical setting: 97% reported they enjoyed the drawing tasks.
- EU CE mark
- Quality procedure for medical device manufacturing, following ISO 13485 QMS standard
- Signed up partner for launch in the EU retail market for health screening (pharma/retail/HR)
- FDA 'Breakthrough Device Designation for the differentiation between Parkinsonian and other (more benign) tremor disorders. NMP will be the only device with tremor differentiation claims on the market
- FDA Data Development Plan
- Signed up US Key Opinion Leaders for clinical trial: Prof Irene Litvan at UCSD
- Signed agreement with J&J for use of NMP in CAR T-cell therapy to detect early signs of neurotoxicity (adverse effect).
- Very recently, an agreement with a well know pharmaceutical enterprise was offered for use in longitudinal monitoring (at present unannounced).

Clinical sites, where NMP was implemented (first in research and now becoming reference centres) include the following UK National Health Service Hospital Trusts: Northumbria, Cumbria, Gateshead, Oxford University NHS hospitals UK. Additional implementation and validation for CE marking took place at the University Medical Centre Groningen (Netherlands), Mater Misericordia university hospital in Dublin (under leadership of Prof Timothy Lynch) and Neuromedic (private neurology clinic in Serbia, under leadership of Prof Stankovic).

Endorsement letters from clinical specialists are available as appendix: EndorsementLetters_Final.pdf

A cost effectiveness study took place in the UK NHS. The model compared a diagnostic pathway for patients presenting with symptoms of a movement disorder in primary care, under current standard of care to the same pathway with Manus NMP added. Addition of NMPs allowed earlier diagnosis leading to earlier use of effective therapies with benefits to patient health. Healthcare costs were also impacted with the addition of costs of Manus and earlier treatment, as well as reduction in initial diagnostic costs due to less use of other resources such as imaging. Health benefits were estimated in units of quality-adjusted life years (QALY), a measure that combines life expectancy with health-related quality of life weighting.

Initial model results indicate that the addition of Manus would increase QALY per patient by around 0.02, while increasing healthcare costs by around £50 per patient. The incremental cost-effectiveness ratio, defined as the additional cost to the health service for each additional QALY gained from implementing the intervention, was estimated to be £4,813, which is well within standard cost-effectiveness thresholds in the UK NHS (£20,000 or £30,000). Thus, Manus would be considered a cost-effective addition to standard care in the UK NHS.

Attached Files:

- 5 NMP journal papers merged into one file.pdf

Why this solution/product is innovative, the broad implications for future research, and/or how it will improve the human condition

The NMP innovative concept enables healthcare professionals (HCPs) to test for impairment of the brain's extrapyramidal system that controls accurate movements in a non-invasive way by highly accurately analyzing movement recordings. This is possible with highly accurate sensors together with clinical tasks and ground breaking biomarker extraction tools that quantify subtle movement symptoms - that cannot be seen/interpreted with the naked eye – and added complex AI for decision support.

This is a unique concept. Whilst widely available wearables measure activity and gross motor skill (course measurements) when the patient is away from the clinic, NMP measures very subtle symptoms that cannot easily be seen or interpreted with the naked eye by the HCP. NMP helps the HCP see and interpret these complex symptoms, expressed as biomarkers, and then provides decision support, using AI.

For the first time, this enables a faster diagnosis with increased differential diagnostic accuracy compared with the current standards of care. This was confirmed with FDA breakthrough designation, making NMP the first aid to diagnosis in Parkinson's.

Challenges addressed include miniaturization of electronics, development of signal processing tools and AI, requiring 10 years of clinical studies for development and validation and productization into an easy-to-use device. Tablet PC, cloud computing and increasing acceptability of AI have supported the productization. Key opinion leaders are now accepting NMP as an aid to diagnosis.

The NMP implementation has enormous impact potential both in the developed world as well as in the developing world. NMP can aid the specialist diagnosis: Distinguishing benign tremors from Parkinson's is problematic and mostly based on subjective clinical examination. Reported accuracy levels of consultant neurologists in early stages, i.e. when patients are symptomatic and the neurologist sees them for the first time, are only 38%-65% [24, 25]. For 75% of the patients, it takes 6 – 24 months to confirm a clinical diagnosis Parkinson's. Brain scans are stressful and intrusive, using radioactive tracers. NMP in EU trials in specialist centers increased accuracy at first appointment for 'difficult to diagnose' from 50% to 80% [26]. Health economic benefits include a reduced number of appointments & faster diagnosis, reduced number of brain scans and patients well for longer (less costly). For the patient it means a step increase in quality of life once on treatment and benefiting from lifestyle adjustments.

In addition, as NMP enables portability, deskilled, Quick and Accurate diagnosis, it opens up opportunities to provide screening in drugstore, urgent care, family practice. Many of the more than 10 million tremor sufferers can be reassured yearly that their tremor is benign, reducing unnecessary specialist referrals; those with a serious movement disorder can immediately be triaged to specialist. Manus' NMP in conjunction with pharmacy retail chains enable a significant and much needed innovation in healthcare to take place. The fact that NMP can be deployed within pharmacies as well as primary care surgeries and specialist clinics – both in diagnostics and treatment (monitoring) and that electronic data records are available, means NMP can function as a 'connector'. It's sphere of influence reaches all players of the patient journey. Data can be shared between the players. This is unique and none of the competitors is active within the whole patient pathway.

The overall patient journey starts with becoming aware of first symptoms that develop further over time. This then continues with a (sometimes long) process of diagnosis with typically multiple assessments by clinicians from various background and often at least one brain scan. Post-diagnosis the journey continues with a long process (typically 10+ years) of treatment.

Together with the patient support organisations, awareness can be created for the disease and its symptoms. The patient support organisations can point patients at pharmacies and the NMP solution available there.

Clinicians don't always have the time to explore and implement new tests and it's often not in their power to change SOPs without endorsement from outside parties who govern standards of care, which forms a barrier to adoption. However, the trusted pharmacists can perform patient assessment in a very efficient way. They typically have SOPs as well as trained staff. Notably, pharmacies and clinicians are already working more and more closely together. An example is MD village being acquired by Walgreens to increase their clinical footprint.

Data provided by the pharmacist is typically trusted by the physician and test records can be provided to the physician to support diagnostic assessment. Specialist treatment can be supported by symptoms monitoring in the pharmacy as input to specialist treatment optimisation. UCB pharma is taking an interest in NMP and envisioning placing it in pharma.

Pharmacists are trusted not only by clinicians, but also patients and can play an important role in the patient journey. They know what illnesses their clientele is suffering from and when pharmacists pick up the phone to their clients, the clients will listen. In the example of Medispa in Italy, this allows them to engage clients in their database in prevention screening.

Manus NMP combined with pharmacists has the potential to streamline the pathway and improve efficiency. NMP with digital data becomes an enabler to the other players in the patient journey, including the clinicians and pharmaceutical companies providing treatments via clinicians.

NMP is also the first device that is sufficiently sensitive for the early detection of Immune effector cell-associated neurotoxicity syndrome (ICANS) – also called neurotoxic events – which frequently occurs as adverse effect of CAR T-Cell cancer treatment. It is widely known there is a need for an objective, reproducible, easy-to-use, and practicable tool that can be used by all health care providers and possibly caregivers to recognize and assess ICANS in the inpatient or outpatient setting [29]. The earliest manifestations of ICANS include tremor, dysgraphia, general deterioration of fine motor skill and impaired attention [27,28,29]. NMP can detect the subtle symptoms with high sensitivity and monitoring of patients following CAR T-cell treatment reduces the risk of progression of ICANS, which could otherwise lead to death. Innovation giant J&J awarded a cash prize for the NMP solution and signed an agreement for the trialling and implementation of NMP to detect ICANS.

Endorsement letters from clinical specialists are available as appendix: EndorsementLetters_Final.pdf

Beyond the currently proven NMP utilities, there are additional important utilities on the horizon. A proof of concept was completed with Prof David Owens at the University of Edinburgh for the detection of an 'extrapyramidal threshold' in patients with schizophrenia being treated with antipsychotic medication. This provides the opportunity to optimize (usually minimize) the dose of antipsychotics to let patient benefit from the medication without suffering side effects that can cause severe movement problems, frequently leading to social anxiety and job loss due to uncontrolled movements.

An additional innovation in development for use in deep brain stimulation is real time feedback during circle drawing for feedback on the efficacy of deep brain stimulation in the treatment of tremor.

An parallel innovation is Manus developing an NMP version to support the early detection of Alzheimer's disease and other forms of dementia and Innovate UK awarded £600,000 of grant funding.

New cognitive tasks were developed and NMP enables for the first time to test both cognitive and motor skill assessments. The Alzheimer's screening test implementation in primary care and or pharmacy retail will enable to streamline the pathway in an analogue fashion to the current tremor/Parkinson's differentiation test. The ultimate goal is to implement NMP as a neuro screening tool that measures both cognitive and movement problems and pinpoint first whether there is either cognitive or movement problem or both (such as in Lewy Body dementia) and then triage to the right specialist.

These R&D projects towards future utilities are phased in the product road map in line with the Company strategy. The Company's current focus is on commercializing tremor differentiation and aid to diagnosis use product.

The pharmaceutical industry will benefit from NMP as follows:

- In patient recruitment (e.g. confirm Parkinson's/other movement disorder or avoid a second problem, such as a functional movement disorder with psychiatric origin)
- Detection of adverse effects in trials
- Use as an end point in trials and the higher accuracy than UPDRS rating scales has the potential to reduce the number of patients and/or number of follow up appointments to prove efficacy.
- Longitudinal monitoring of motor (and cognitive) symptoms during treatment

Manus has just completed a new round of investment and expanded the senior management team to further innovate in healthcare as follows:

1. Complete US FDA clearance with trials, following Breakthrough Device designation.
2. Increase sales efforts into the EU tremor differentiation market with partner Medispa, who have integrated NMP into their Prevention suite health screening service: Prevention Suite- integrated platform of health services (prevention-suite.com). Once FDA clearance has been obtained, the Company will focus on US business development and reduce EU focus.
3. The Company will expand its US operations and for that purpose, the founder and CEO is relocating to the US.
4. In addition, clinical sales and key opinion leader collaboration are being expanded and a VP sales was appointed.
5. The fifth focus area towards healthcare innovation is implementing the US market access plan with US partnering organizations, including reimbursements towards widespread adoption within the next 5 years. These healthcare innovation activities will achieve the ultimate aims of streamlining patient pathways, creating patient health benefits & reducing anxiety of patients/carers/family, while enabling enormous cost savings for healthcare providers.

Attached Files:

- EndorsementLetters__ManusFinal.pdf

Please provide appropriate references (ie Pubmed links)

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