

**R&D Update
And Biomarker Driven Strategy**

HERANTIS

PHARMA

26th October 2021

Antti Vuolanto COO & Henri Huttunen CSO

Our mission is to break boundaries of standard therapeutic approaches. Our drug candidates aim to revolutionize the treatment of Parkinson's Disease and other Neurodegenerative diseases.

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Topics We Will Cover

- Biomarkers
- Blood-brain barrier (BBB) Crossing
- Neuroprotection
- Alternative administration routes
- Commercial Opportunity

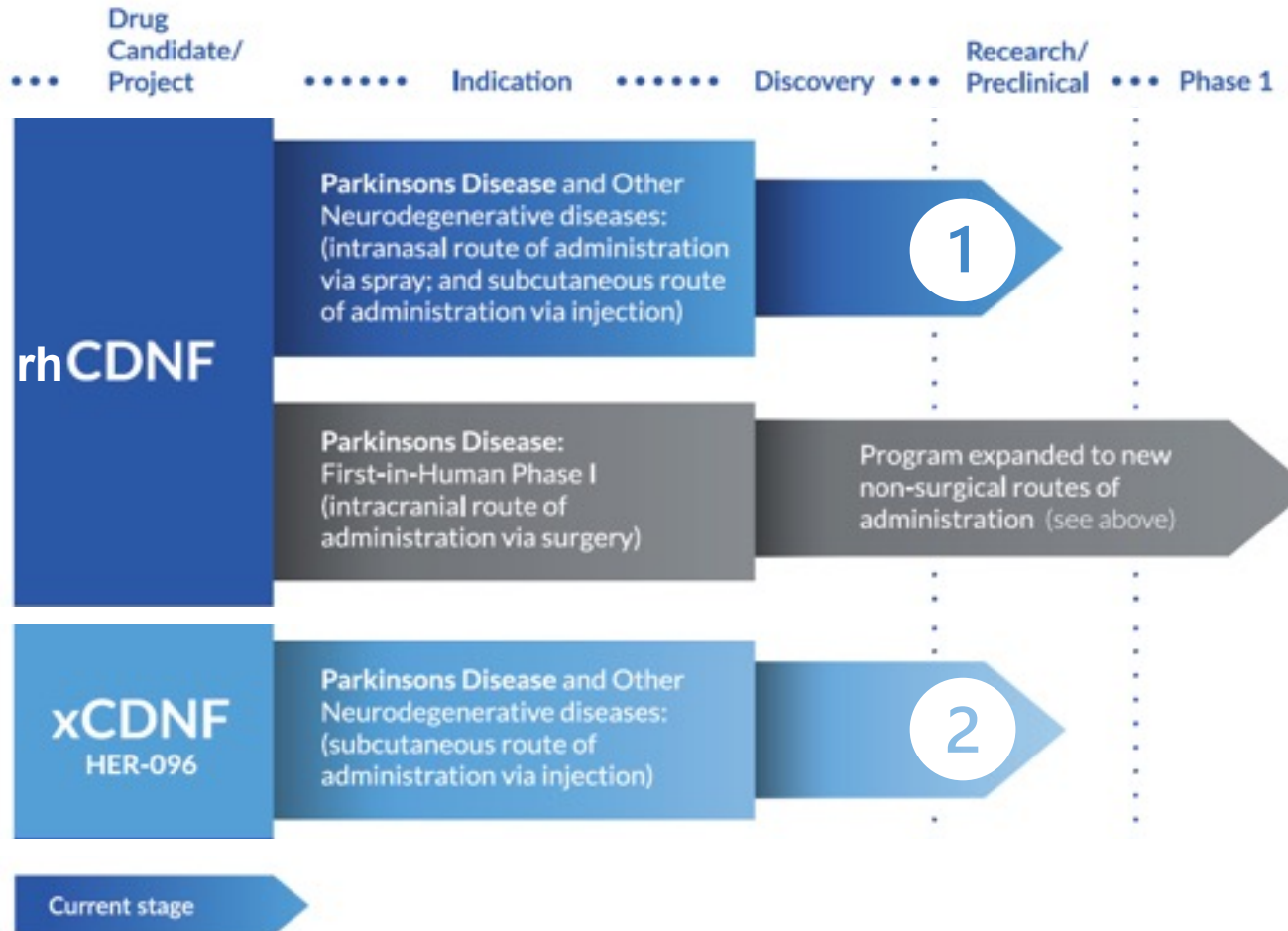
Objective

- Share the progress we are making on biomarkers, non-invasive administration routes, as well as update on blood-brain barrier penetration and neuroprotective data of our assets.

The background of the slide is a deep blue. It features a large, semi-transparent DNA double helix structure that winds across the frame. In the center, a hand in a white lab coat sleeve is pointing its index finger towards the DNA. The word 'Introduction' is written in white, bold, sans-serif font, centered over the hand and the DNA.

Introduction

Herantis Focused On Parkinsons And Other Neurodegenerative Diseases

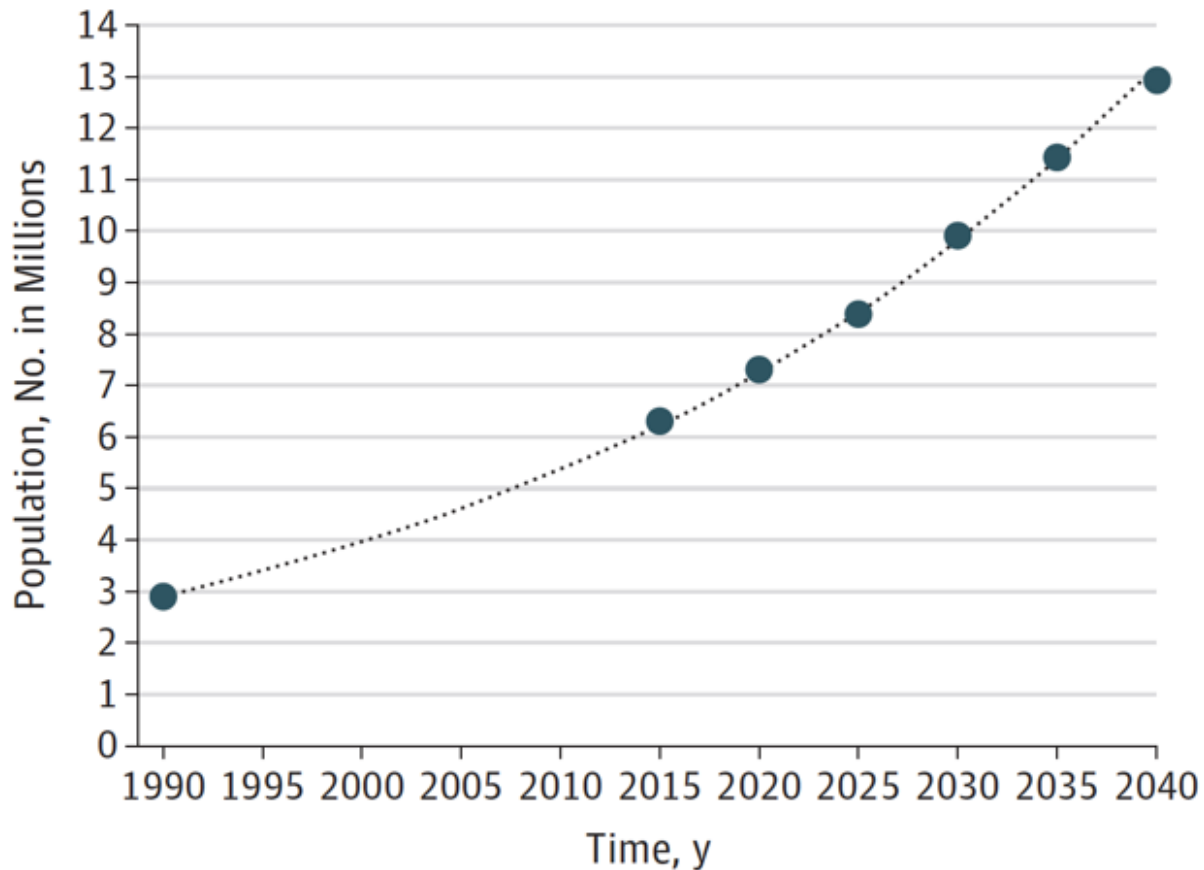


- **Headquartered Helsinki, listed Finland & Sweden**
 - IPO 2014 (Finland) 2019 (Sweden), €67m to date
- **Two programs:**
 - rhCDNF** a **ground-breaking biological** therapy.
Already used **safely** in human Phase I study via surgical intracranial administration; now being developed for follow on Phase I using intranasal route of admin
 - HER-096 (xCDNF)** **innovative and advanced small synthetic** chemical peptidomimetic version of the active parent rhCDNF protein. Combines i. the **compelling MoA** of rhCDNF protein and ii. ability to **cross blood brain barrier** after simple skin injection

CDNF = Cerebral Dopamine Neurotrophic Factor

Parkinson's Disease – Urgent Need For Disease Modifying Treatments

Figure. Estimated and Projected Number of Individuals With Parkinson Disease, 1990-2040

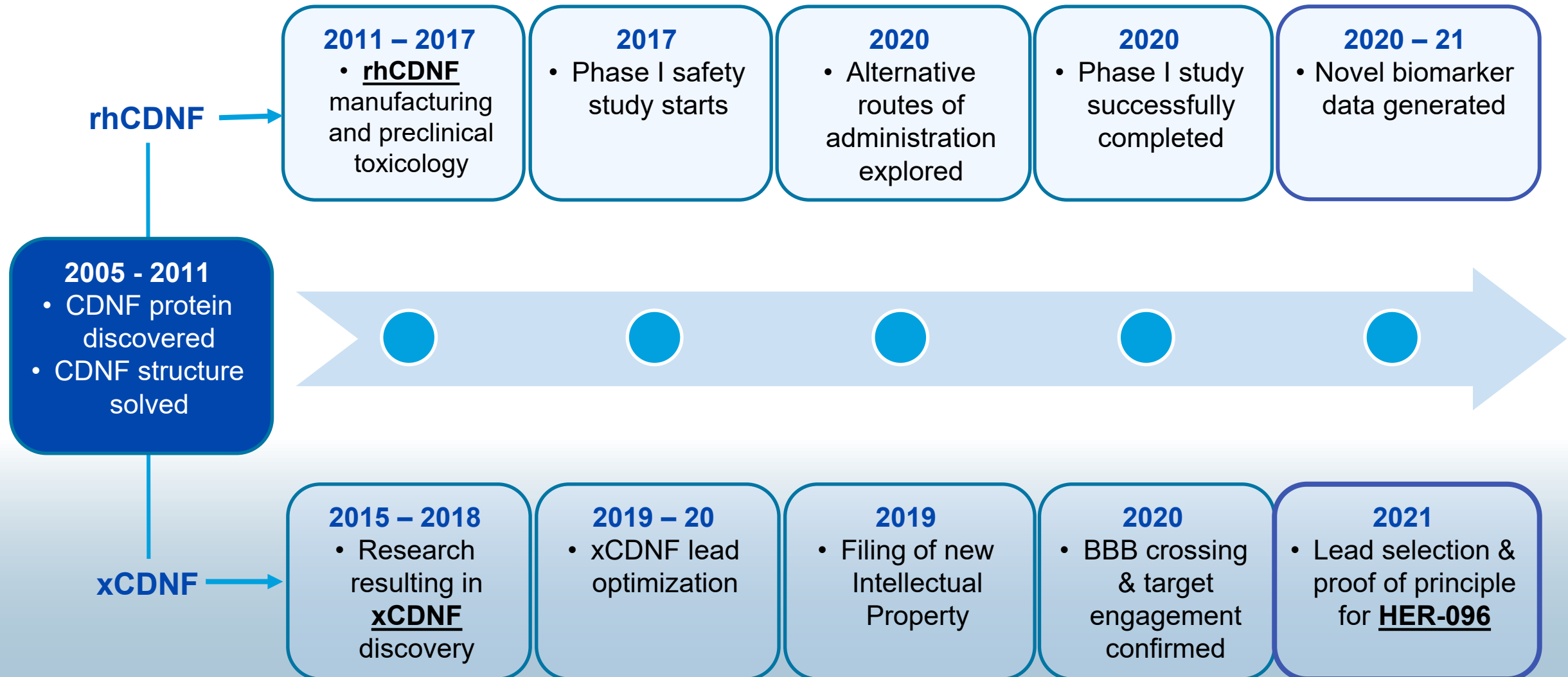


Viewpoint: E.Ray Dorsey, MD, Bastiaan Bloem, MD, PhD

¹ European Parkinson's Disease Association www.epda.eu.com

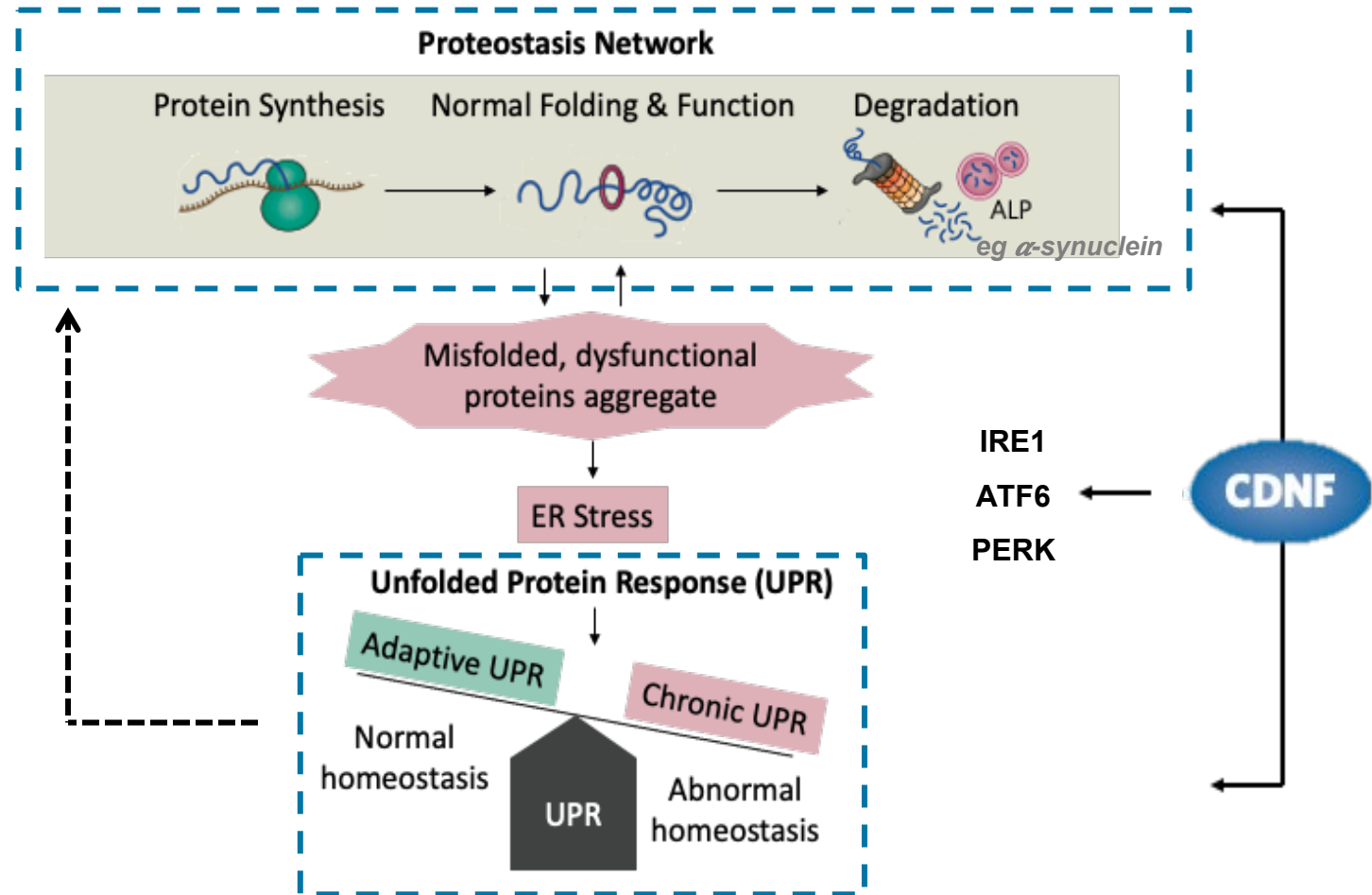
- Exploding incidence of Parkinson's worldwide ... of 'pandemic proportions'
 - combination of man-made and genetic factors
- Massive burden of disease for the world
 - > 10 million patients worldwide, costs €14bn annually EU alone, household costs €20,000/year/patient
- Current treatments wholly insufficient
 - symptomatic only, useful but no affect on disease
 - same mainstay of care, levodopa, since 1950's
- New & successful innovations desperately needed
 - lots of research and pharma investment into PD
 - Herantis rhCDNF and HER096 well positioned in the competitor space

More Than A Decade Of Innovation Coming to Fruition



rhCDNF and HER-096 Targets Core Pathology Of Parkinson's – Proteostasis & Unfolded Protein Response (UPR)

- Proteostasis regulates proteins in body and influences the fate of every protein from synthesis to degradation
- Its failure is implicated with the development of neurodegenerative diseases such as Parkinson's
- ***rhCDNF and HER-096 designed to restore proteostasis via modulation of unfolded protein response (UPR) pathway and promote functional recovery of stressed cells***



Nature BioPharma Dealmakers 2021, <https://www.nature.com/articles/d43747-021-00070-6>

CNS Drug Development is Shifting to Biomarker-driven Development Strategies

- Diseases take a long time to develop, so without biomarkers it can take years to see clinical results
 - Biomarkers provide a window into onset of disease, its progression, and response to therapy
 - Enables ***more rapid & efficient assessment of drug effect, that otherwise could take years***
 - Shortens development times, saves costs
- Recent conditional approval of Biogen's aducanumab in Alzheimer's bodes well for Herantis assets:
 - Biogen: Aducanumab first **disease-modifying drug** approved in Alzheimer's, **biomarkers** key for approval
 - Herantis: CDNF unique **disease-modifying drug** for Parkinson's, strong **biomarker** data generated to date
 - Biomarkers considered of equal importance to clinical observations, regulators starting to value the role of biomarkers and their assessment
- Compelling biomarker data generated in rhCDNF Phase I, and HER-096 development to date
 - Unique in Parkinson's research
 - Provides a strong foundation to build upon, and will be a key component of our programs moving forward

The background of the slide features a blue-toned image of a hand in a white lab coat sleeve, pointing towards a large, detailed DNA double helix structure. The DNA helix is rendered with visible base pairs and sugar-phosphate backbones, creating a sense of depth and scientific focus.

The New Biomarker-Driven Strategy

Why Biomarker Development has Become so Important in Drug Development?

- Mechanism-based, targeted therapies have successfully paved the way for precision medicine in oncology
- All therapeutic areas are transitioning to and leading pharma companies have already adopted biomarker-driven clinical trials models
 - McKinsey & Co recently estimated that 30-40% of novel drugs in the pharma pipeline are developed in conjunction with a biomarker
 - >99% of neurodegeneration trials have been unsuccessful to date
- Biomarker tests can compress drug development timelines, increase patient response rates and reduce development costs
- Clinical trial success rates are 3x higher when a biomarker strategy is implemented

Incorporation of Biomarkers to the Drug Development Process is Critical for Success

NO BIOMARKER STRATEGY

Biomarkers not co-developed with the therapeutic



Traditional patient selection methods compromise patient response rates



Increased risk of failing to meet clinical endpoints



8.4% clinical trial success rate*

BIOMARKER-LED

Biomarker assays developed to characterize disease models and monitor response to therapy



Stratified patient populations increase drug response rates



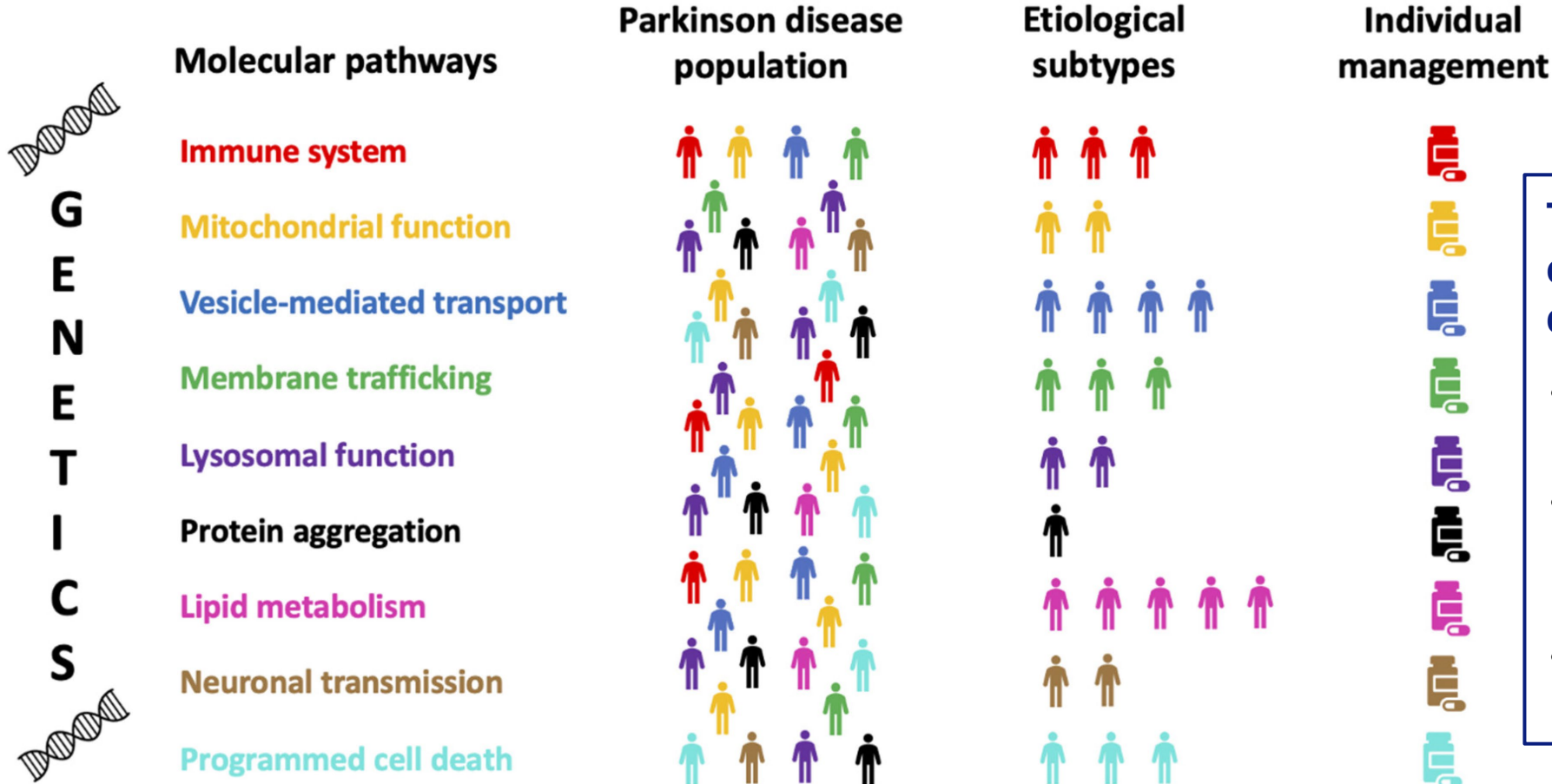
Rich treatment efficacy data generated, delivering deeper insights on the mechanism of action



25.9% clinical trial success rate*

* Anon, 2016. Biomarker tests for molecularly targeted therapies.

Parkinson's Disease is a Heterogenous Disease with Multiple Etiological Subtypes



Types of biomarkers used in clinical development of disease-modifying therapies

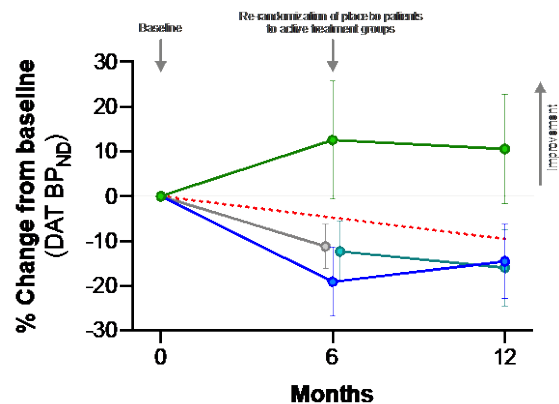
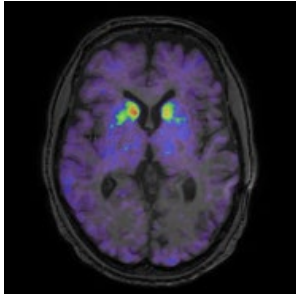
- Biomarker-driven phenotyping for targeted clinical trials
- Pharmacodynamic biomarkers for measuring treatment response
- Prognostic biomarkers to follow disease progression in trials

Reed et al. J. Pers. Med. 11(3): 169, 2021

Three Biomarker Modalities Explored in CDNF Phase 1 Study

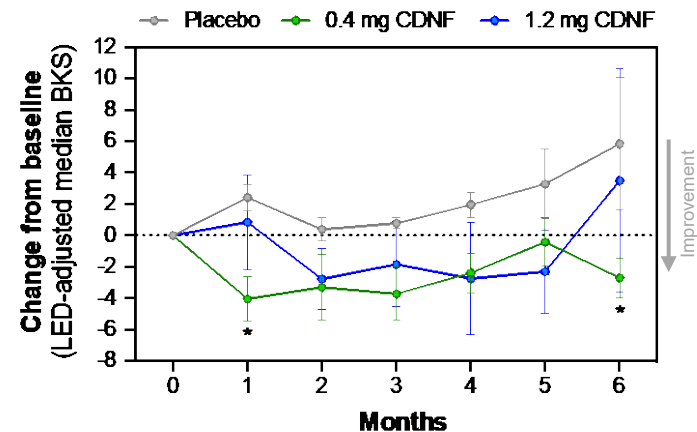
Brain imaging biomarker:

Dopamine transporter
PET imaging



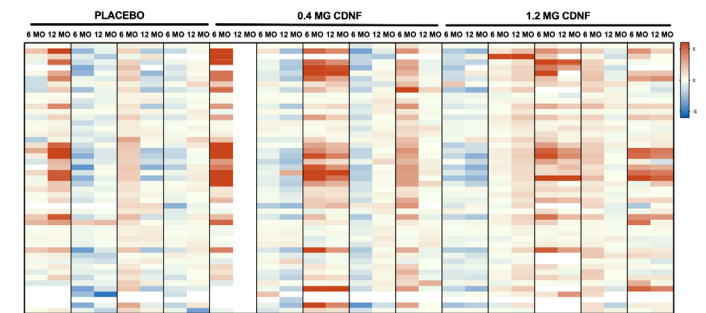
Digital biomarker:

Parkinson's
KinetiGraph (PKG)

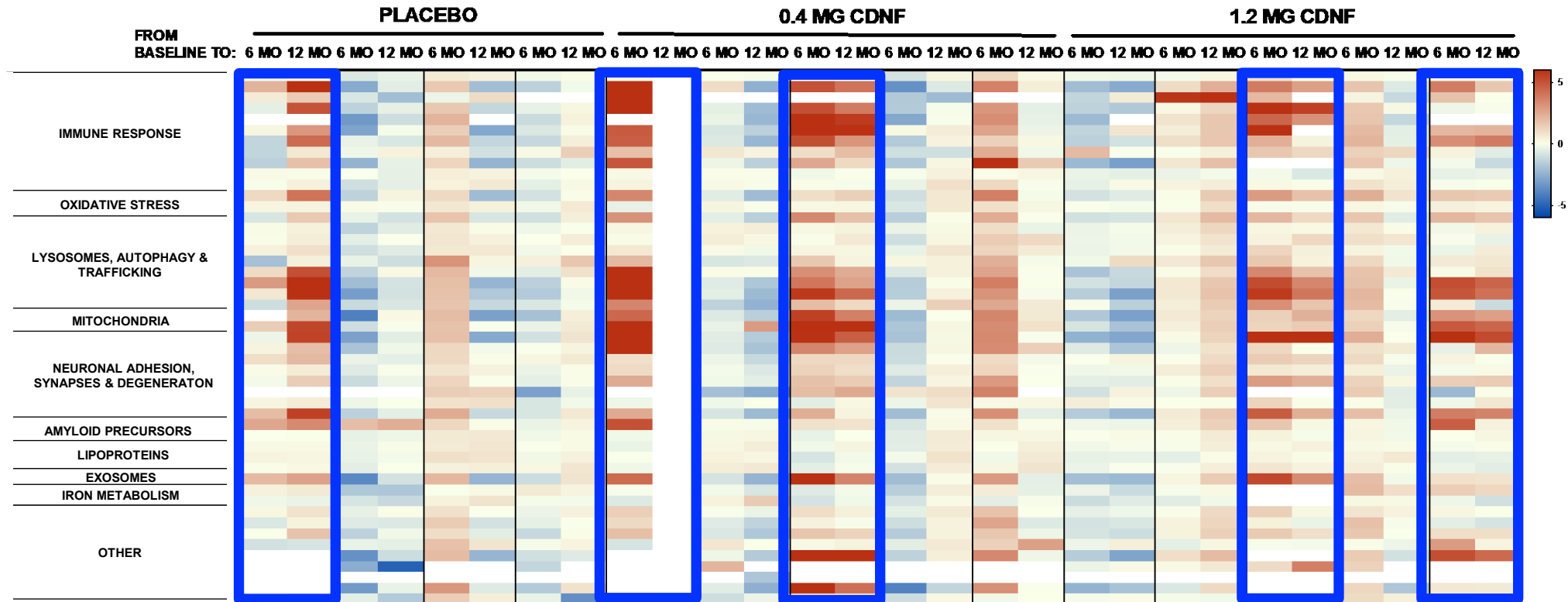


Fluid-based biomarkers:

CSF biomarker
discovery study



Biomarker Discovery Data: Targeted Cerebrospinal Proteomics Study Revealed a Biomarker Fingerprint in PD Patients Receiving rhCDNF



- 20 cerebrospinal fluid markers identified in a subgroup of CDFN-treated patients with moderately advanced Parkinson's disease

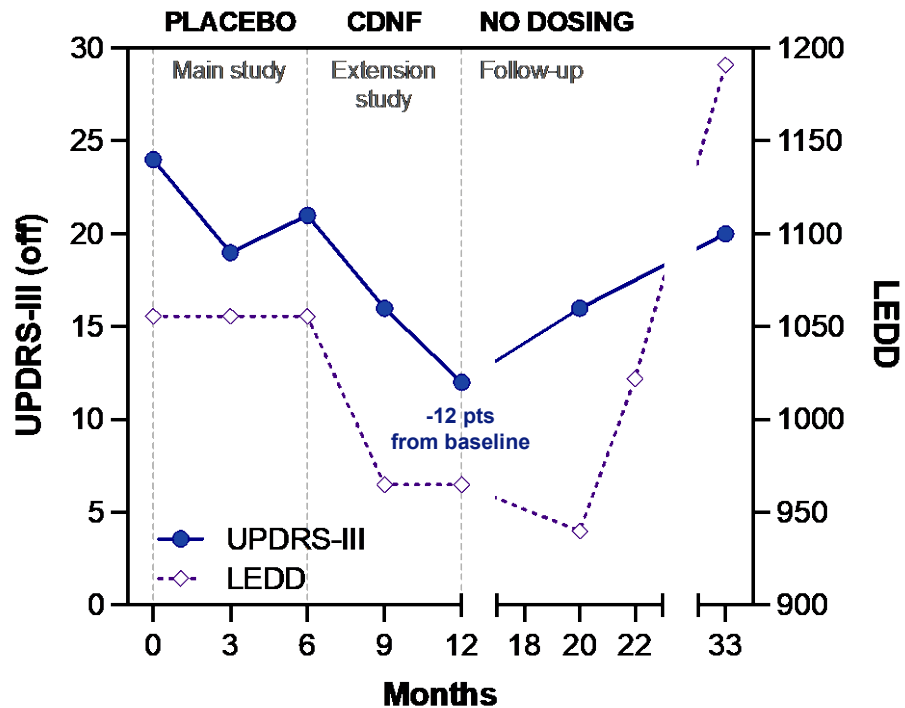
Unpublished data

An Example of a Biological Responder: Clinical Improvement Associated with a Change in CSF Biomarker Profile after Switching from Placebo to rhCDNF

- 62-year old male
- Disease duration: 10 years (from first motor symptoms)
- 6 months placebo, followed by 6 months CDNF

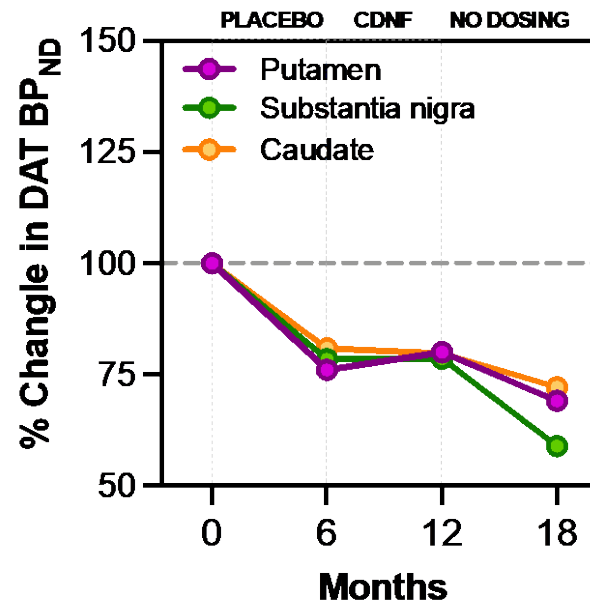
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UPDRS and LEDD



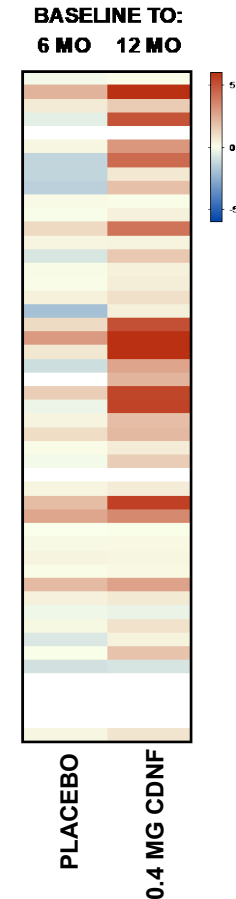
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DAT PET



3

CSF Proteomic profile



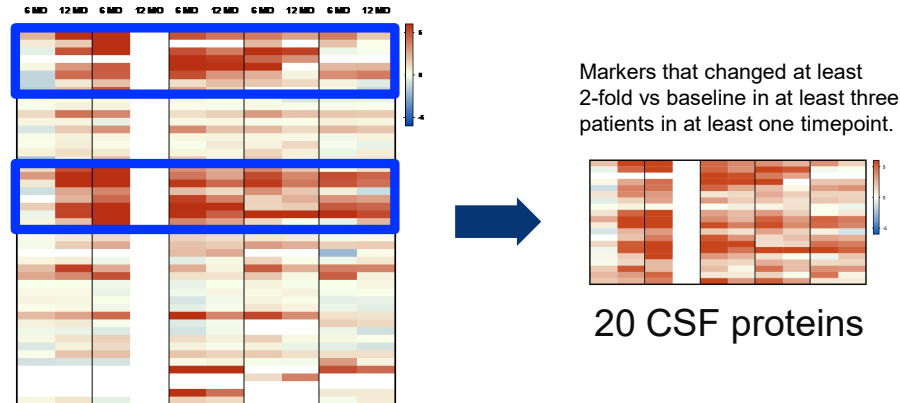
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Genotype: LRRK2 (G2019S)

- The most common mutation in familial Parkinson's but also a common mutation in sporadic Parkinson's.
- Typical manifestations of Parkinson's disease.
- Considered an excellent population for genetically targeted clinical trials in PD.

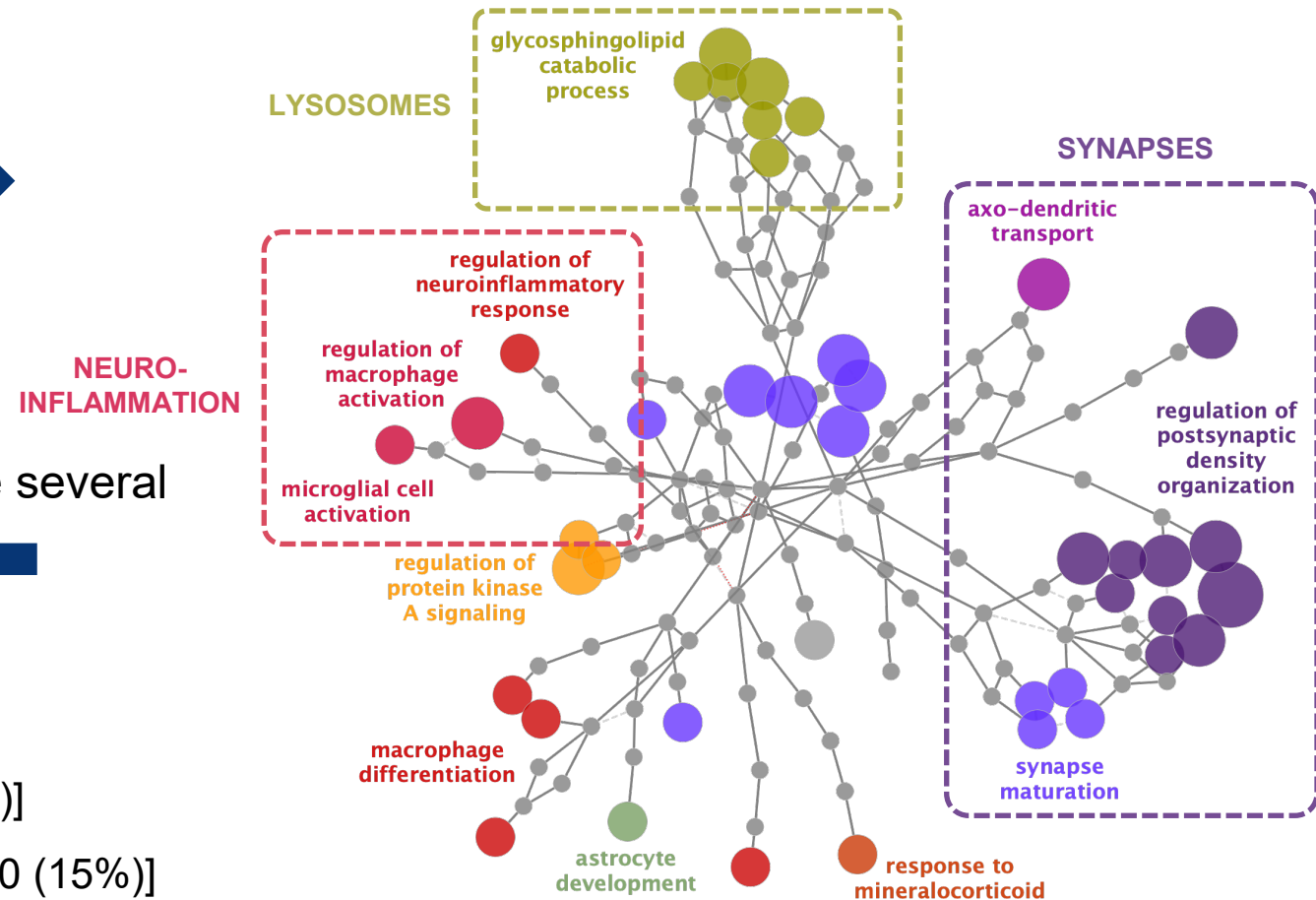
Unpublished data

A Biomarker Signature: The Twenty CSF Proteins Showing Similar Pattern of Change in the Biological Responders Have Common Functional Links



- The 20 CSF proteins that change in concert share several functional associations:
 - Lysosome function/autophagy [6 of 20 (30%) markers that changed in concert in "responders"]
 - Immune response, neutrophil activation [6 of 20 (30%)]
 - Neuronal cell adhesion and synapse assembly [3 of 20 (15%)]

Functional association: Gene Ontology (GO) term enrichment analysis of the 20 CSF proteins



Pathway analysis done in Cytoscape v3.8.2 with ClueGO plugin
(Bindea et al. Bioinformatics 25:1091–1093, 2009).

Unpublished data

Herantis Launches a New Program to Develop & Leverage Biomarkers for Disease-Modifying Trials in Parkinson's Disease

- Key elements of the new biomarker program:
 - Build on the existing biomarker discovery data generated in rhCDNF Phase 1 study: via further verification and validation develop a multimodal biomarker approach for clinical proof-of-concept studies
 - Build a strong team with track record and vision to execute biomarker-driven clinical development
 - Goal to complete biomarker development for Phase 1b/Phase 2a clinical studies with rhCDNF & HER-096 (current estimate: to start Phase 1b/2a in 2024)
- Two arms of biomarker-led R&D work:
 - Preclinical biomarker research (e.g. development of ultrasensitive assays, explore candidate biomarkers in preclinical models of Parkinson's, and biomarker sample libraries)
 - New clinical study planned to start in 2022:
 - Observational biomarker study: new cohort of early Parkinson's patients, incl. genetically defined subgroup
 - Collect data on natural variation of biomarkers in early Parkinson's and verify candidate biomarkers in a clinically relevant cohort
 - A network of four clinical sites and key collaborators and partners has been established

Herantis' Scientific Team Expanded With a CNS Biomarker Expert



- Dr. Kira Holmström recruited as the Head of Biomarker Research at Herantis Pharma, starting 26 Oct 2021
- Ph.D. in Cognitive and Behavioural Neuroscience from International Max Planck Research School, University Tübingen, Germany
- Previously at Orion Pharma (Preclinical and clinical biomarker lead in neurodegenerative and rare disorders)
- Adjunct Professor of Molecular Neuroscience, University of Helsinki and University of Tampere
- Previous academic research positions at National Institute of Health (USA), University College London (UK), University Tübingen (Germany), University of Helsinki and University of Tampere (Finland)
- Extensive research experience immersed in neurodegenerative disorders, from molecular neuroscience to in vivo behavioural models and biomarker development

New Scientific Advisory Board Nominated to Guide Biomarker-Driven Development



- **Anders Gersel Pedersen**, M.D., Ph.D.
- Chairman of the Board
- Globally renowned and respected expert in CNS drug development. Previously Executive Vice President of R&D at Lundbeck for 19 years. Currently on multiple boards including e.g. Genmab.



- **Daniele Bravi**, M.D., Ph.D.
- Specialist Neurologist in movement disorders
- Renowned CNS disease expert. Previously Vice President, Chief Medical Officer, Vice President of Drug Development at Lundbeck USA



- **Alberto Espay**, M.D., professor
- Professor and chair of the University of Cincinnati James J. and Joan A. Gardner Family Center for Parkinson's Disease and Movement Disorders
- Globally renowned expert and author in biomarker-driven clinical development in movement disorders
- Chair of Movement Disorder Society's Technology Task Force



- **David Dexter**, Ph.D., professor
- Associate Research Director at Parkinson's UK and Professor of Neuropharmacology at Imperial College London
- Renowned expert in mechanisms of cell death and neuroprotection in Parkinson's disease



Update on rhCDNF and HER-096 Programs

Update on rhCDNF Formulation Development for New Route of Administration

- Development of formulation for intranasal (nose-to-brain) delivery of rhCDNF is progressing as planned; despite some delays preclinical data set on brain distribution is expected to be complete during 1H 2022
 - More than 50 candidate formulations developed and tested, selected formulations taken to performance testing using state-of-the-art in vitro model of human nasal epithelium and to in vivo testing
 - Preclinical collaboration initiated with an intranasal delivery device manufacturer
- Exploration of utility of subcutaneous rhCDNF in new indications
- Process proof-of-concept stage reached with generation of CDNF protein nanoparticles, further process optimization on-going (collaboration with Nanoform Finland Plc); expected to progress to in vivo testing in 1H 2022 (release 09 Sep 2021)

Update on HER-096 Preclinical Development

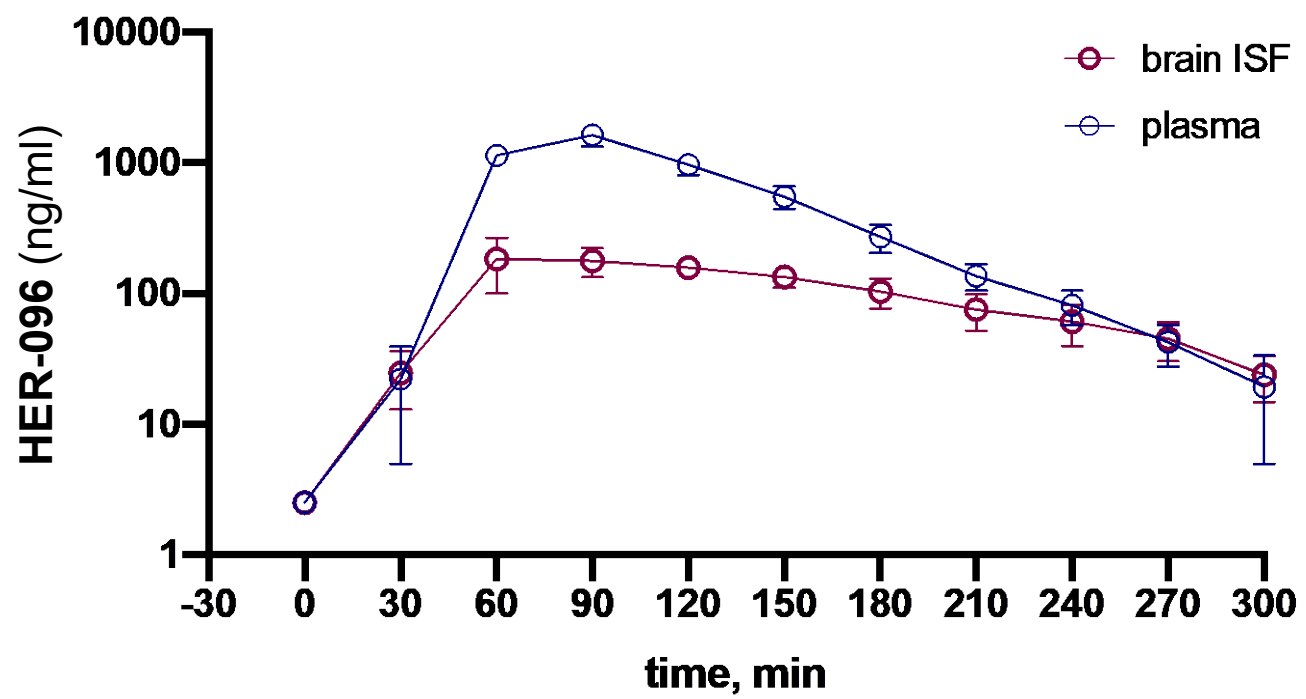
- Lead optimization completed, preclinical candidate (HER-096) selected (release 31 May 2021)

Progress during 2H 2021

- Compound salt form selected
- Contract manufacturer selected and first research-grade batch manufactured
- Large batch for GLP toxicology studies is being manufactured
- Nonclinical toxicology studies started
- Target engagement confirmed in a preclinical animal model of Parkinson's disease
- Dose finding and biomarker exploration studies proceed as planned
- Goal of first-in-human Phase 1 study initiation in early 2023 on track

Subcutaneously Administered HER-096 Effectively Penetrates the Blood-Brain Barrier with Therapeutic Concentrations and Extended Half-life in the Brain

DUAL (BRAIN AND PLASMA) MICRODIALYSIS STUDY IN MICE



$K_{p,uu,brain} = 0.216$

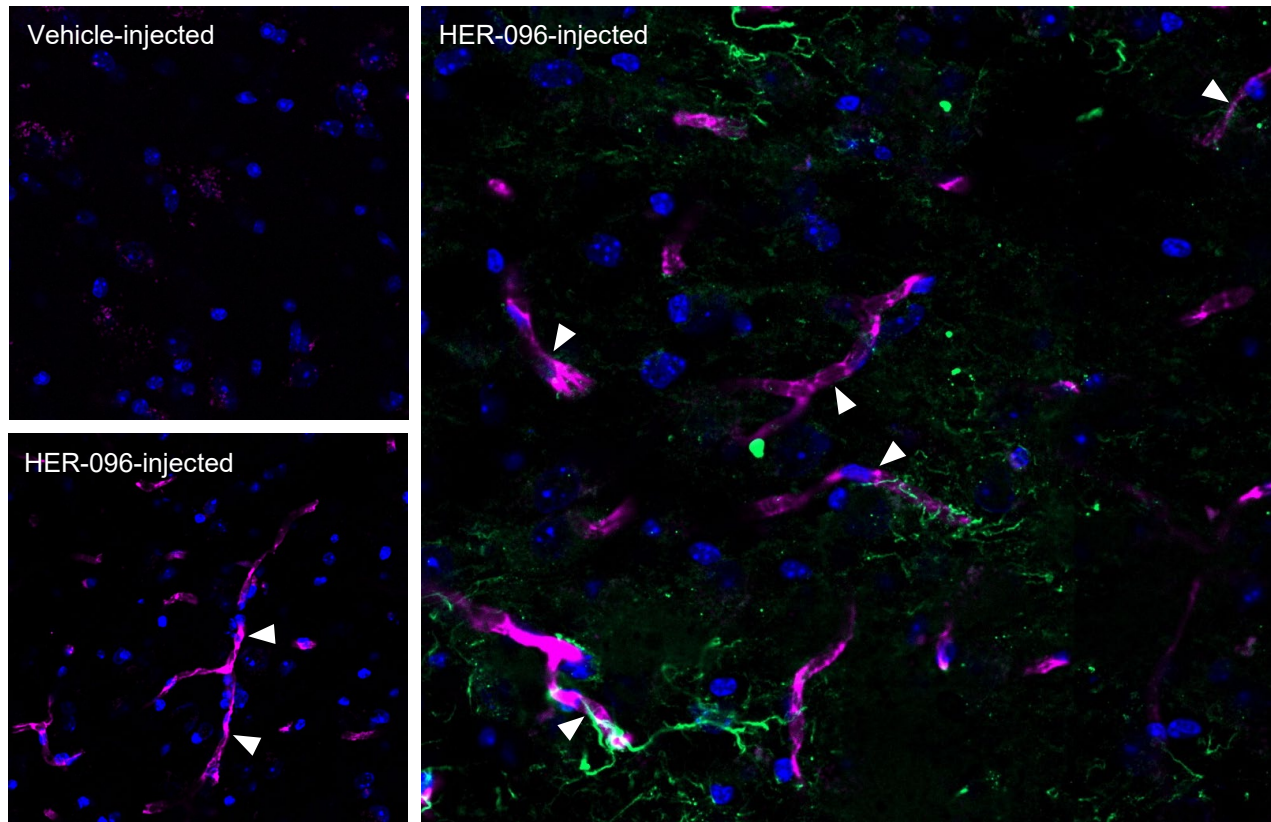
Brain ISF $T_{1/2} = 1.3\text{ h}$

Brain ISF $C_{max} = 185\text{ ng/ml}$ ($> 180\text{ nM}$)
Brain ISF $AUC_{(0-inf)} = 529\text{ ng/ml}\cdot\text{h}$
Brain ISF $T_{1/2} = 1.3\text{ h}$

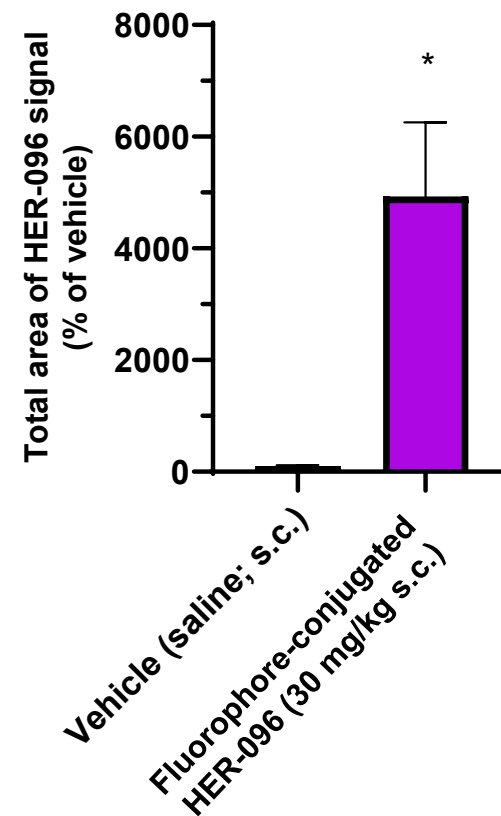
Plasma $C_{max} = 1637\text{ ng/ml}$
Plasma $AUC_{(0-inf)} = 2450\text{ ng/ml}\cdot\text{h}$
Plasma $T_{1/2} = 0.5\text{ h}$

STUDY: Mice with microdialysis probes placed in the striatum and jugular vein were subcutaneously injected with 5 mg/kg HER-096 and microdialysate samples were collected for 5 h at 30 min intervals. The concentration of unbound compound was detected by LC-MS/MS and the values normalized by recovery efficiency of the microdialysis filter determined by in vitro experiments. n=4. $K_{p,uu,brain}$ = brain-to-plasma ratio of unbound compound.

Uptake of HER-096 by Multiple Cell Types of the Brain Following Subcutaneous Injection



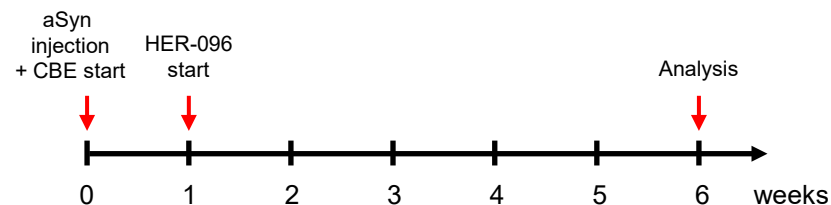
Nuclear marker Fluorophore-conjugated HER-096 GFAP (astrocyte marker)



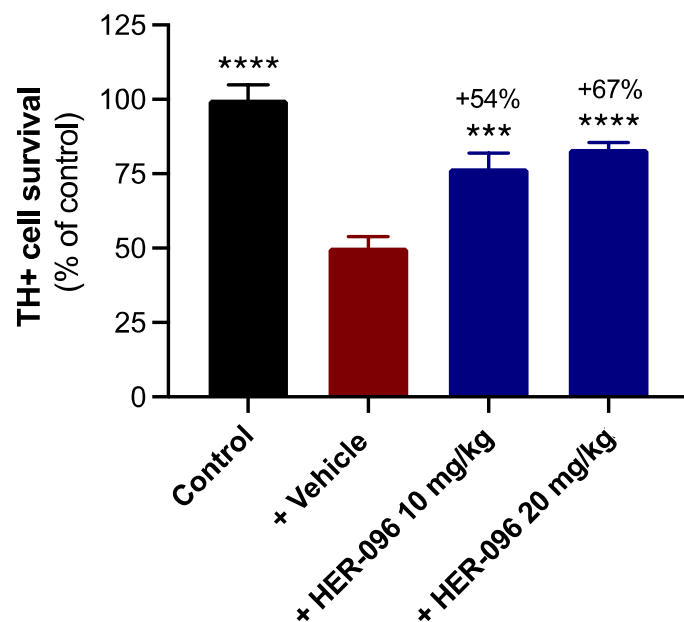
* p<0.05 versus Vehicle; t-test

- Fluorophore-conjugated HER-096 s.c. administered (30 mg/kg) to healthy mice. Tissues collected and analyzed at 90 min post-injection.

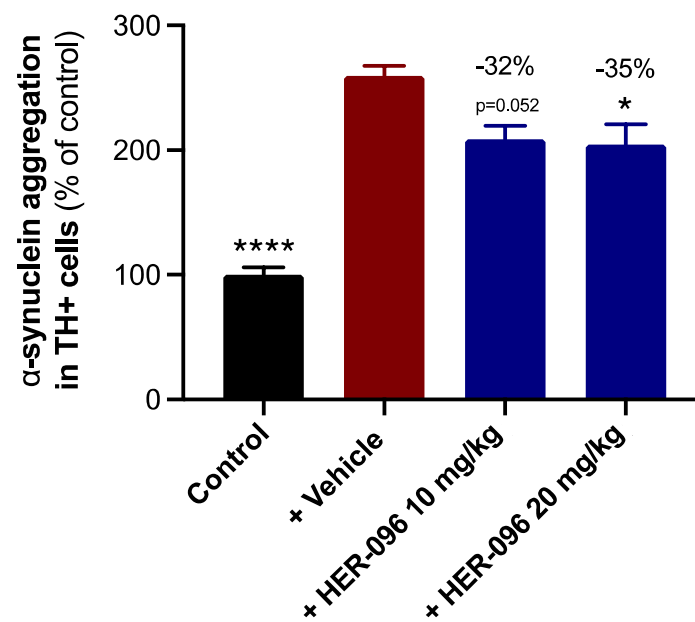
HER-096 Shows Robust Disease-modifying Effects in an Alpha-synuclein Mouse Model of Parkinson's Disease



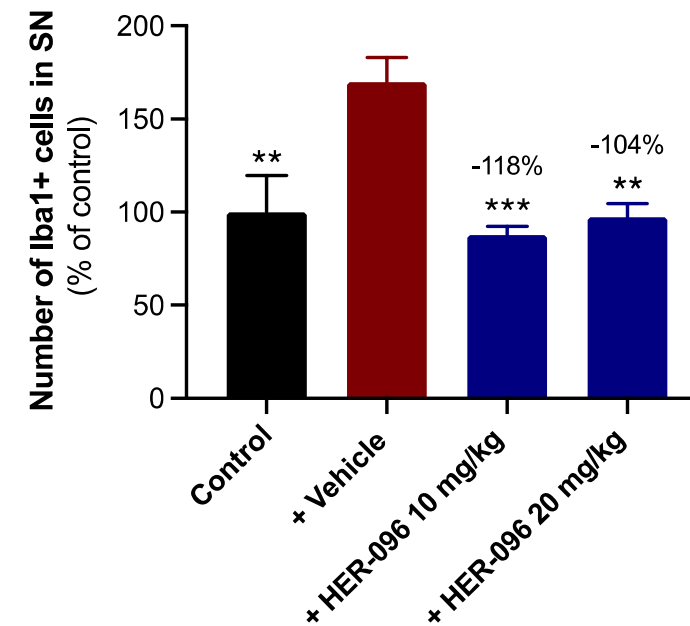
Nigral Dopamine Neuron Number



Alpha-synuclein Deposition



Neuroinflammation

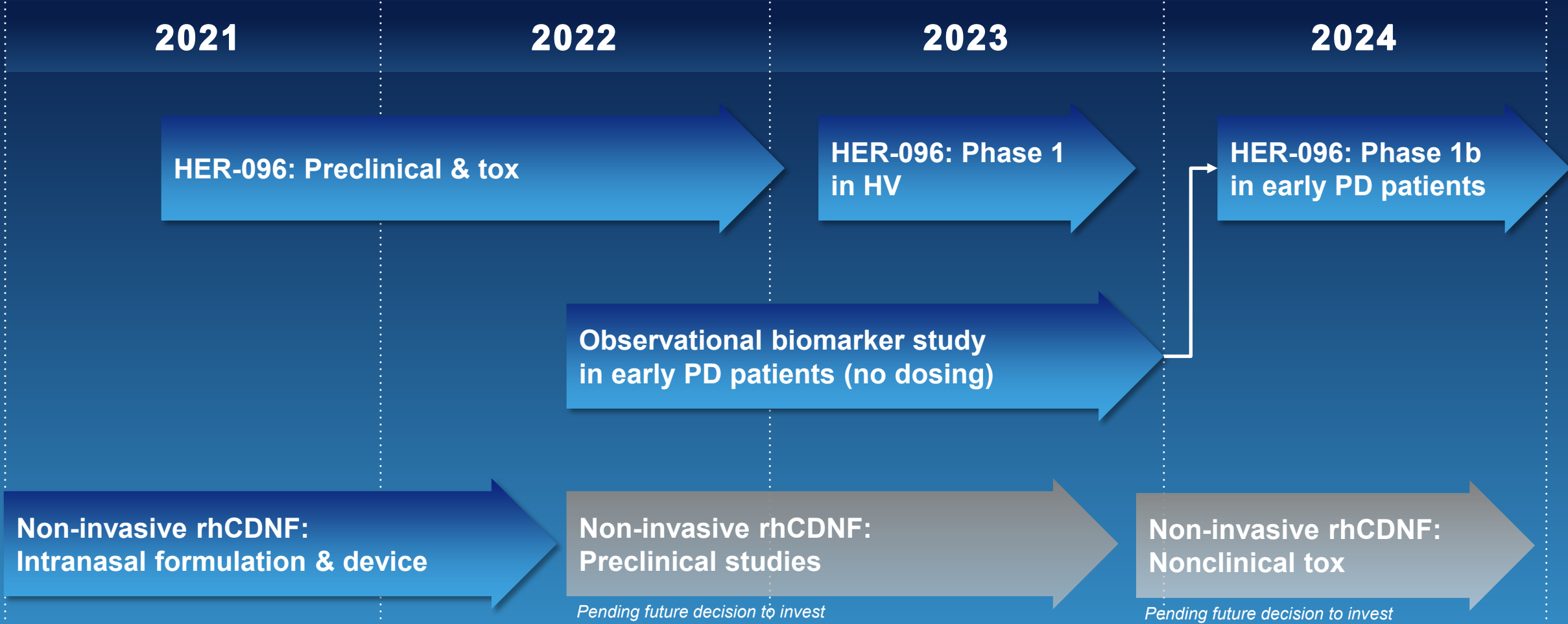


Compound dosing (s.c., 3 times a week) started 7 days after aSyn injection and continued for 5 weeks

Unpublished data

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Planned Development Timelines for HER-096 and rhCDNF



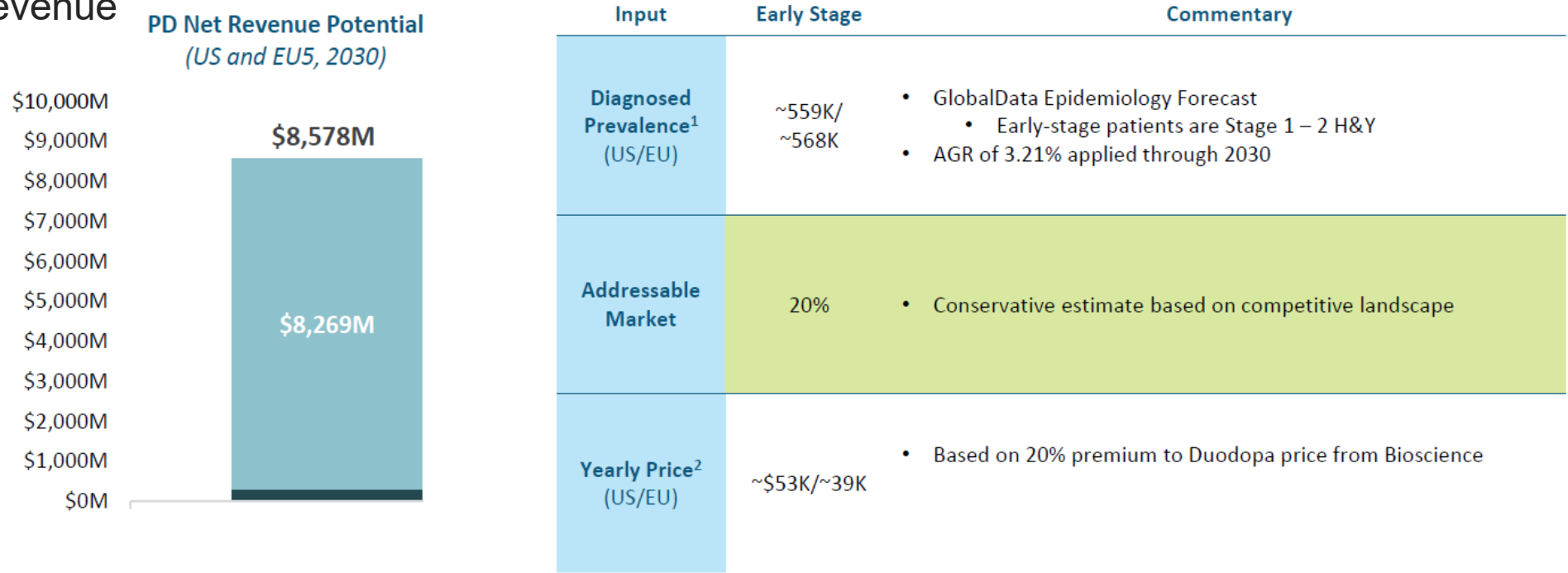
The indicated timelines are subject to change, depending on availability of funding, finalisation of clinical trial design, regulatory interactions, Covid, etc.
HV = healthy volunteers; PD = Parkinson's disease

The background of the slide is a deep blue. It features a large, semi-transparent DNA double helix structure that winds across the frame. Overlaid on this is a hand in a white lab coat sleeve, with the index finger pointing towards the center of the image. The text 'Market Opportunity' is centered over the hand and DNA.

Market Opportunity

Enormous Commercial Potential For rhCDNF &/Or HER-096 In Parkinsons

- Disease modifying treatment rhCDNF/HER-096 for Parkinson’s disease could reach **more than €8 bn** in total annual revenue



- Herantis business model is focused on **partnering** with large pharma; we **continue to dialogue with potential partners**
- Timing of deals typically anytime following pre-clinical through to clinical proof of concept (after Phase I/II)
- **Size of deals anywhere from \$0.5bn to \$1.5bn** eg Merck/Yumanity, Roche/Prothena, GSK/Alector

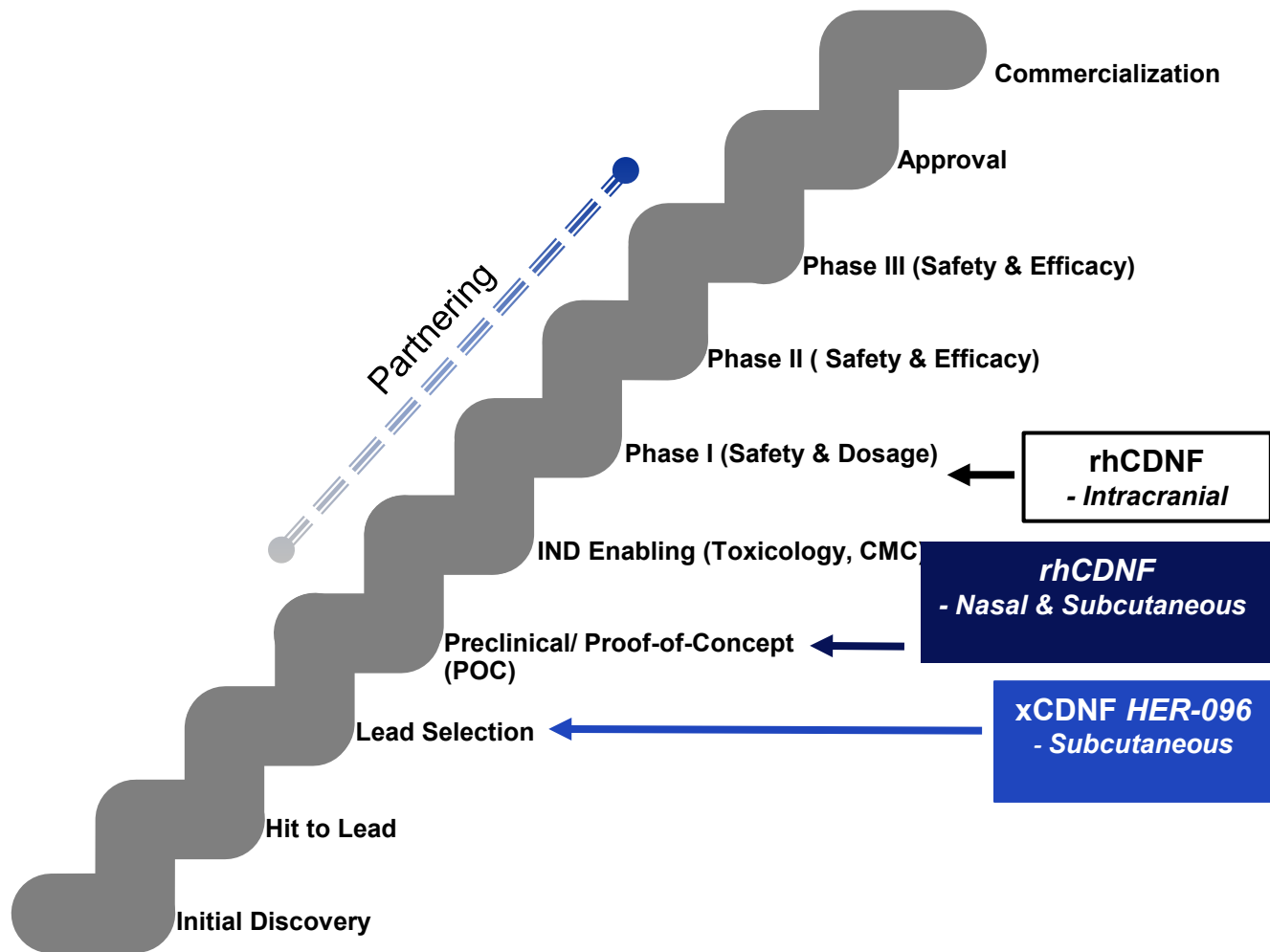
Desperate & Amplifying Need For Disease Modifying Therapies (DMT's) Like rhCDNF and xCDNF

- Successful innovation urgently needed to address Parkinson's pandemic
- Other drug classes eg mAbs hold/held a lot of promise for neurodegenerative diseases, but facing challenges
 - target α -synuclein protein preventing aggregation and potentially halting Parkinsons progression
 - cinpanemab (Biogen 2020), venglustat (Sanofi 2021) discontinue
 - prasinezumab (Roche) continuing following 'just enough evidence' to advance into further development
- Challenging for similar pipeline candidates, and amplifies that a major unmet need remains in bringing DMTs & neuroprotective agents to market, currently dominated by symptomatic treatments
- ***Herantis' rhCDNF and xCDNF HER-096 well positioned in competitor space***

The background of the slide is a deep blue. It features a large, semi-transparent DNA double helix structure that winds across the frame. A hand, also semi-transparent and in a similar blue tone, is positioned in the center, with the index finger pointing towards the DNA structure. The overall aesthetic is scientific and professional.

Conclusion

Timelines & Some Of The Key Planned Milestones



2H 2021	Parkinson's Disease and other neurodegenerative diseases	rhCDNF:	Intranasal administration formulation milestones
2H 2021	Parkinson's Disease	xCDNF (HER-096)	Pre-clinical efficacy and additional PoC milestones
1H 2022	Parkinson's Disease and other neurodegenerative diseases	rhCDNF:	Pre-clinical efficacy and PoC milestones
1H 2022	Parkinson's Disease	xCDNF (HER-096)	IND enabling and toxicology milestones
2H 2022	Parkinson's Disease and other neurodegenerative diseases	CLINICAL:	Observational biomarker study in PD patients



Program Development
Milestones

Summary

- **Unparalleled biomarker data, and clear biomarker program ahead**

- *Strong impact on markers of disease; clear correlation with clinical & imaging improvements*

- **Potent neuroprotection**

- *Restores proteostasis, needed for neuronal survival, convincingly crosses BBB*

- **Significant market opportunity**

- *PD pandemic is multi \$bn need, intense need for neuroprotective agents, successful innovation*

- **Rich potential newsflow**

- *Several near and medium term milestones anticipated en route to clinic*

Focus moving forward is to shape our development programs to further identify the biological and biomarker based Parkinson's populations that most benefit from CDNF, establish new and innovative research paths that fit our rhCDNF and HER-096 assets.

**R&D Update
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Marking A Decade of Successful Research on CDNF

Thank You!