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CDNF Phase I 12-month topline results: Safety, UPDRS and DAT PET data

15 September 2020

www.herantis.com

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Agenda

01 **CDNF:**

- The Disease
- The Treatment
- The Study
- The Data

02 **Conclusions & Next Steps**

03 **Q & A**

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The Disease

Parkinsons Disease (PD) An Incurable Debilitating Illness

- An incurable brain disease caused by degeneration of dopaminergic neurons in midbrain
- Massive medical need with 7-10 million patients worldwide, societal costs $25bn US
- Standard of care Levodopa … since the 1960's
- Main symptoms
  - → Tremor usually in the hand or arm
  - → Slowness of movement bradykinesia
  - → Muscle stiffness and rigidity

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The Treatment

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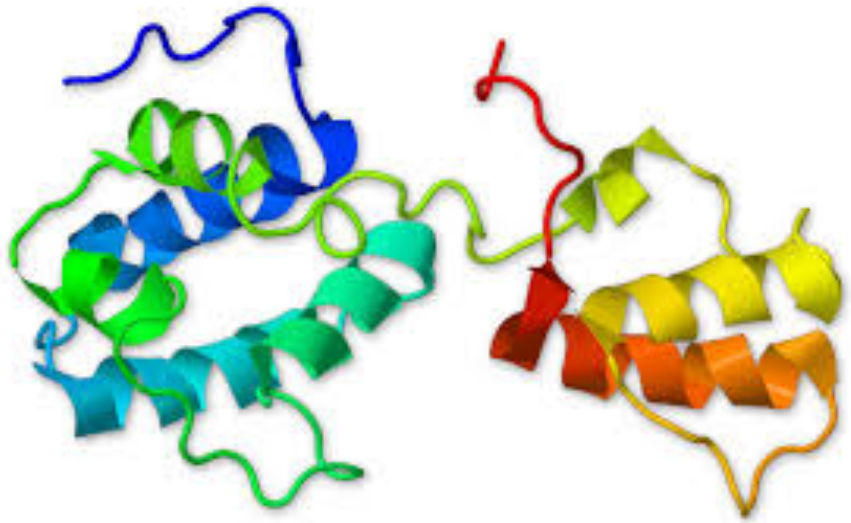
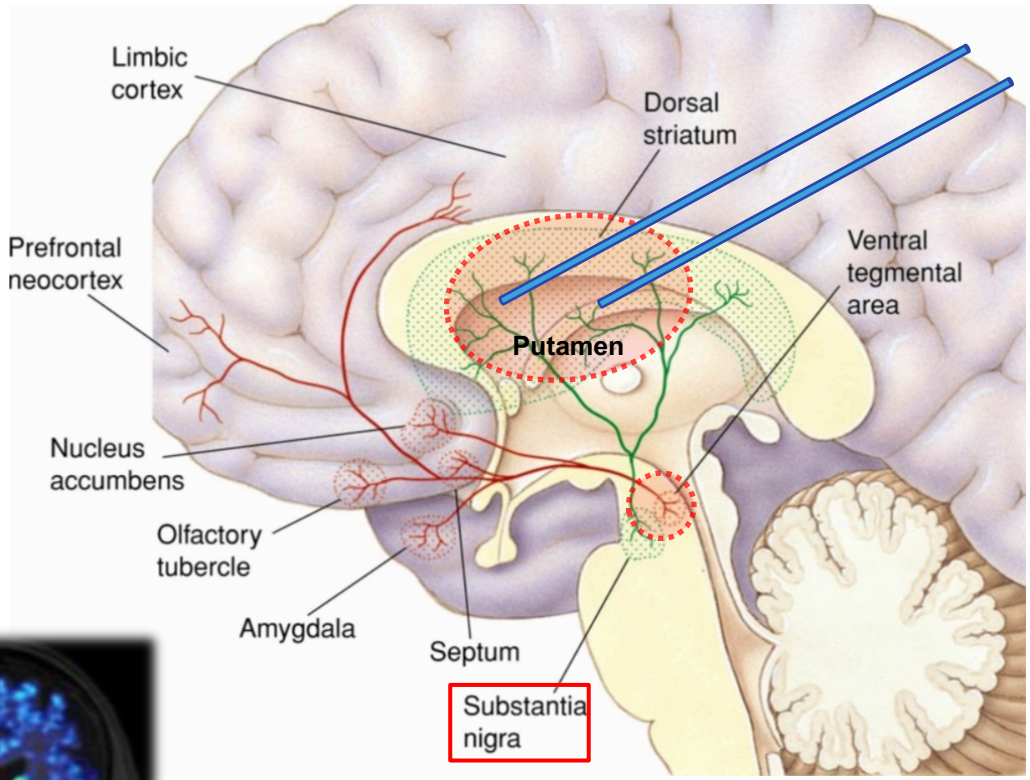
CDNF For Parkinson's Disease (PD)

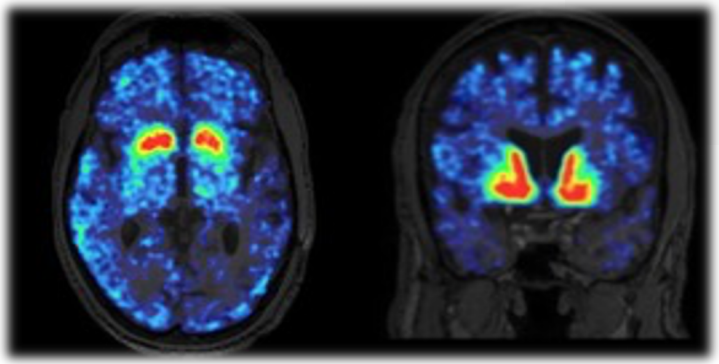
- CDNF is a natural protein whose role is to protect neurons
- Promotes functional recovery of dopaminergic terminals in putamen and the cell bodies in the substantia nigra – the dopamine rich areas of the brain (the nigrostriatal pathway)
- Potential to modify the diseases process – treat the cause not only the symptoms, for Parkinson's Disease as well as other CNS indications



CDNF Administered Directly Into The Brain

- Blood-brain barrier is a common challenge for drug delivery in brain
  - CDNF is dosed directly into the putamen area of the brain with a sophisticated medical device (provided by Renishaw Neuro Solutions (www.renishaw.com)
- Changes in the functional state of the nigrostriatal pathway can be seen with PET imaging





PET imaging using a radioligand binding to dopamine transpoter (DAT)

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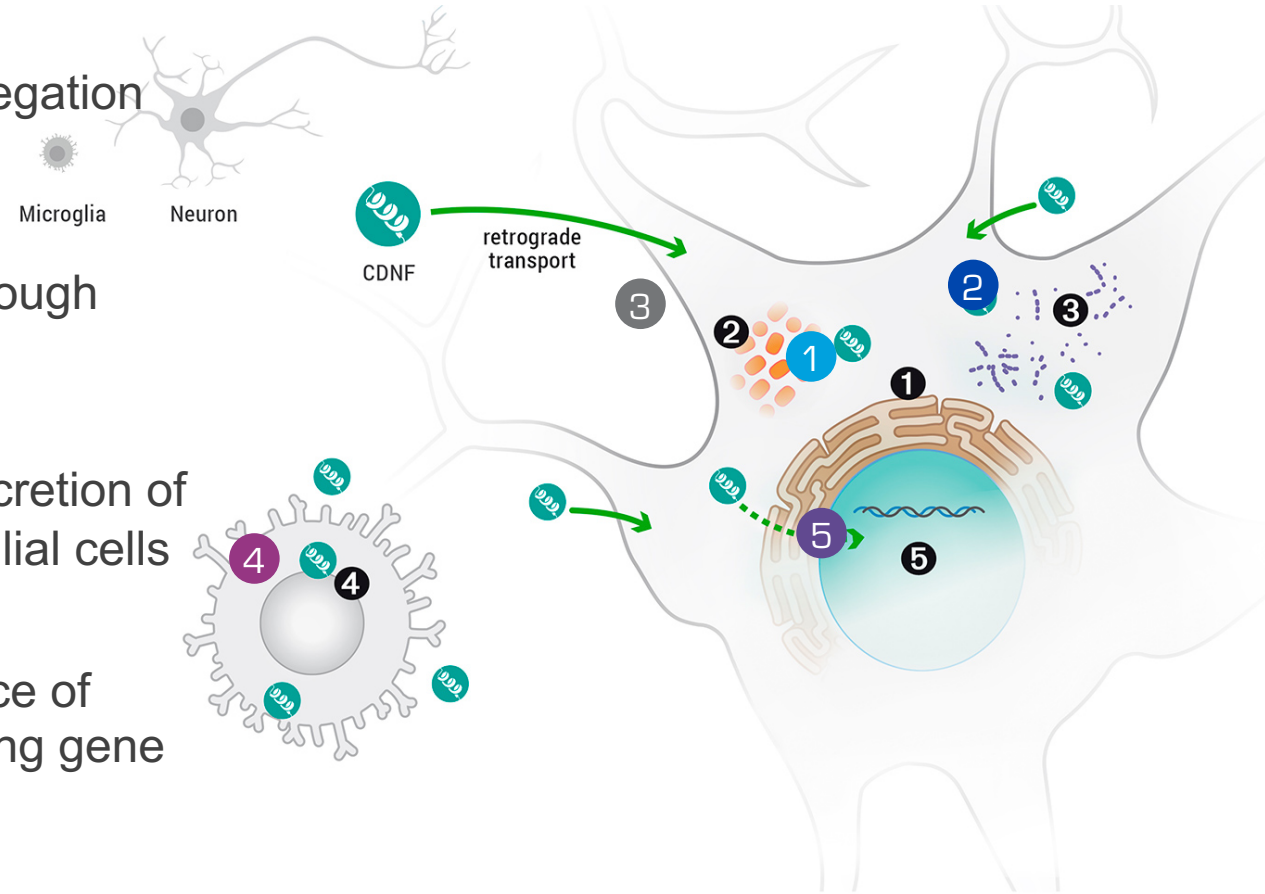
CDNF's Multimodal Mechanisms Of Action

1. Promotes neuronal functionality through reduced endoplasmic reticulum stress
2. Reduces alpha-synuclein aggregation and toxicity
3. Promotes neuronal survival through Protein Kinase B (Akt)
4. Suppresses production and secretion of proinflammatory cytokines by glial cells
5. Supports long-term maintenance of neuronal functions by modulating gene transcription



CDNF: Cerebral Dopamine Neurotrophic Factor; UPR: Unfolded Protein Response

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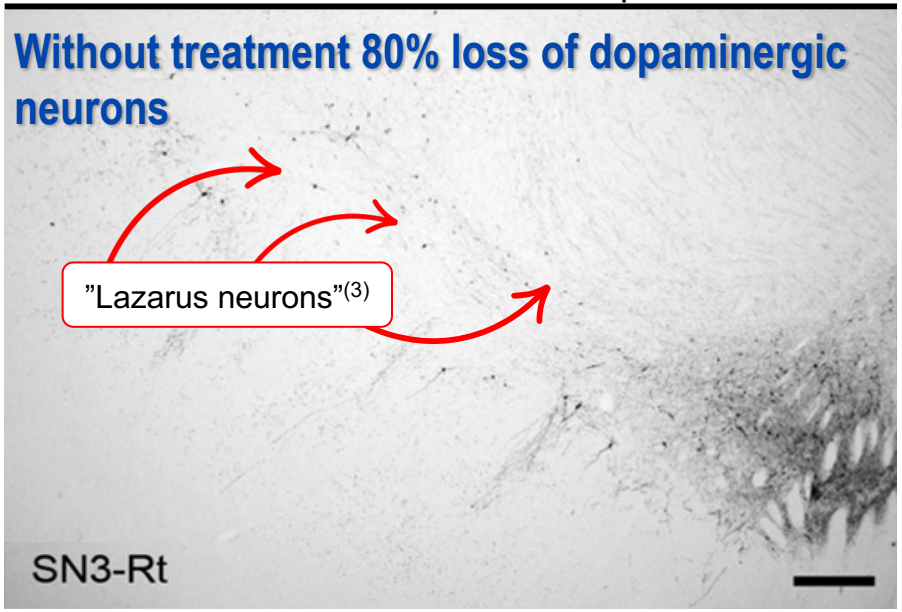
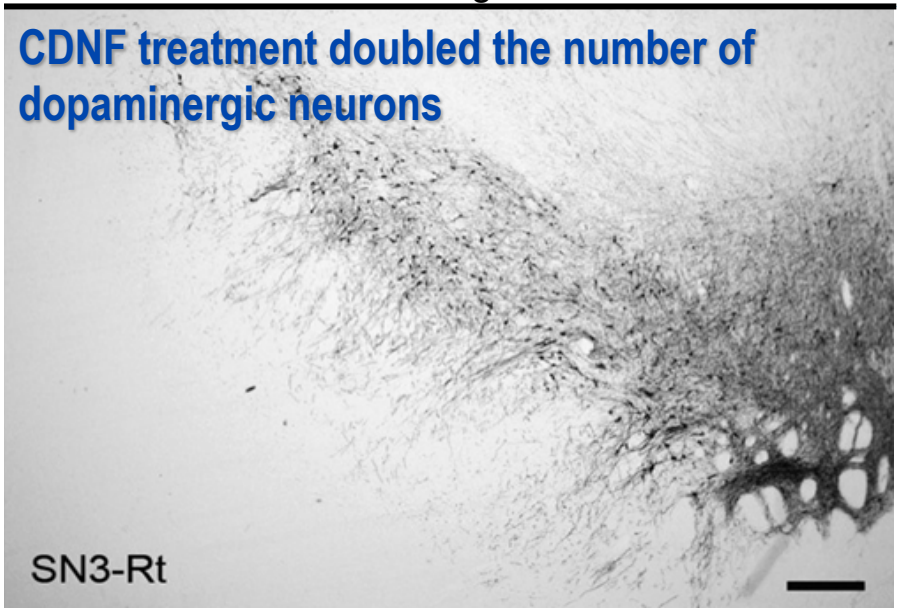
Significant Effect On Neuronal Regeneration In Animals [1]

MPTP lesion model of Parkinson's in primates[2]



- Model: Severe parkinsonism caused in aged primates by MPTP, resulting in significant loss of dopaminergic neurons
- True neurorestoration study: Instead of immediate treatment, the lesions were allowed to mature for six weeks before CDNF administration
- Dark staining in the figure indicates dopaminergic neurons: 80% loss corresponds to advancing PD

CDNF treatment results in significant neurorestoration



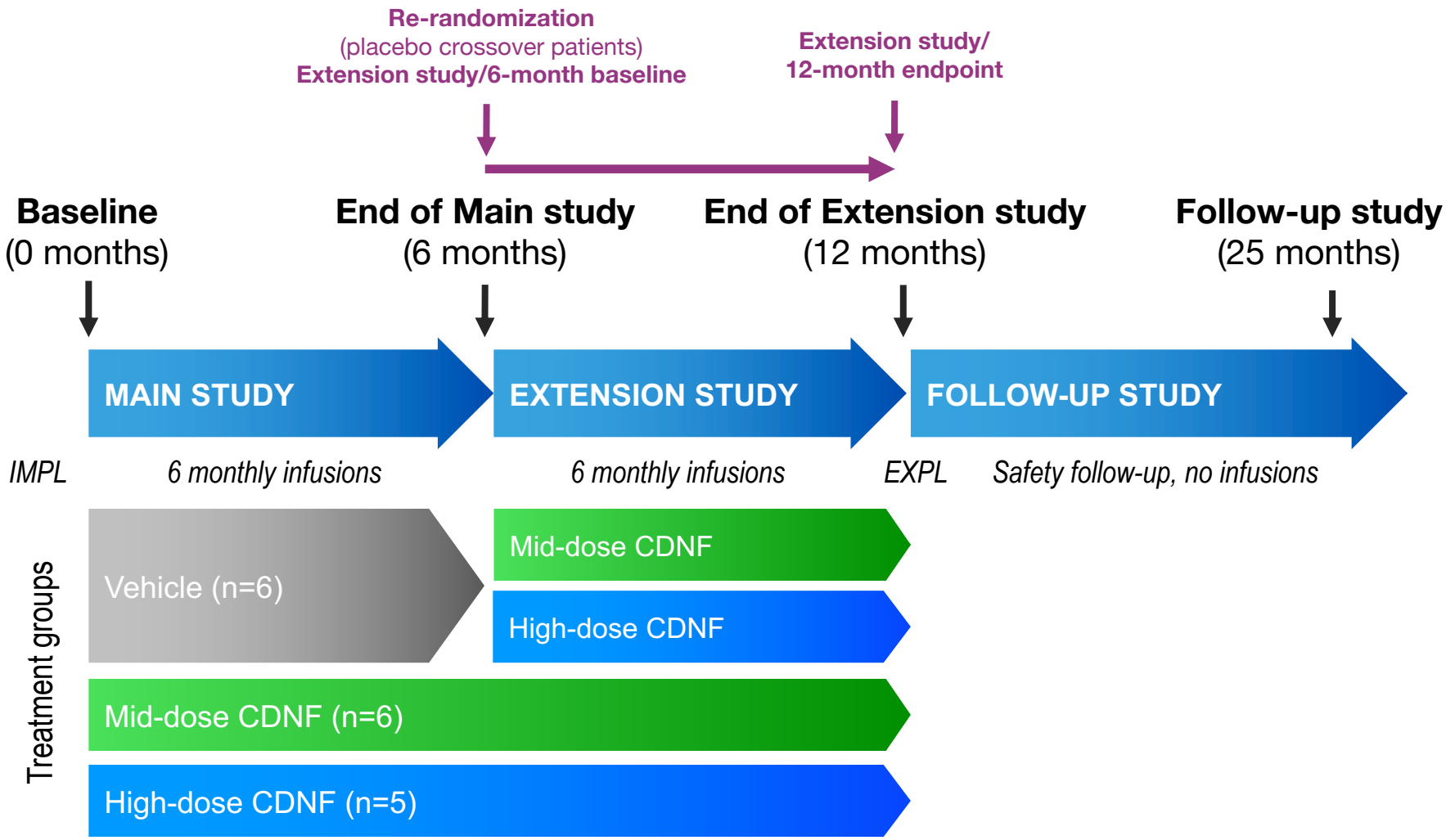
- Three monthly CDNF doses doubled the number of dopaminergic neurons
- Significant improvement in gross motor function, fine motor function, and for the first time in the world, even in non-motor symptoms
- CDNF can help degenerating and dying 'Lazarus neurons' regain their function

1) CDNF: Cerebral Dopamine Neurotrophic Factor; DA neurons: dopaminergic neurons; 2) MPTP: chemical compound that causes permanent parkinsonism; 3) "Lazarus neuros" is the term used by Herantis for degenerating neurons that have lost their phenotype (such as ability to produce dopamine)

Collaboration with University of Helsinki and University of Pittsburgh. Study funded by Michael J. Fox foundation.

The Study

Clinical Study Design: Three Groups, Three Parts



EudraCT number: 2015-004175-73
NCT number: 03295786

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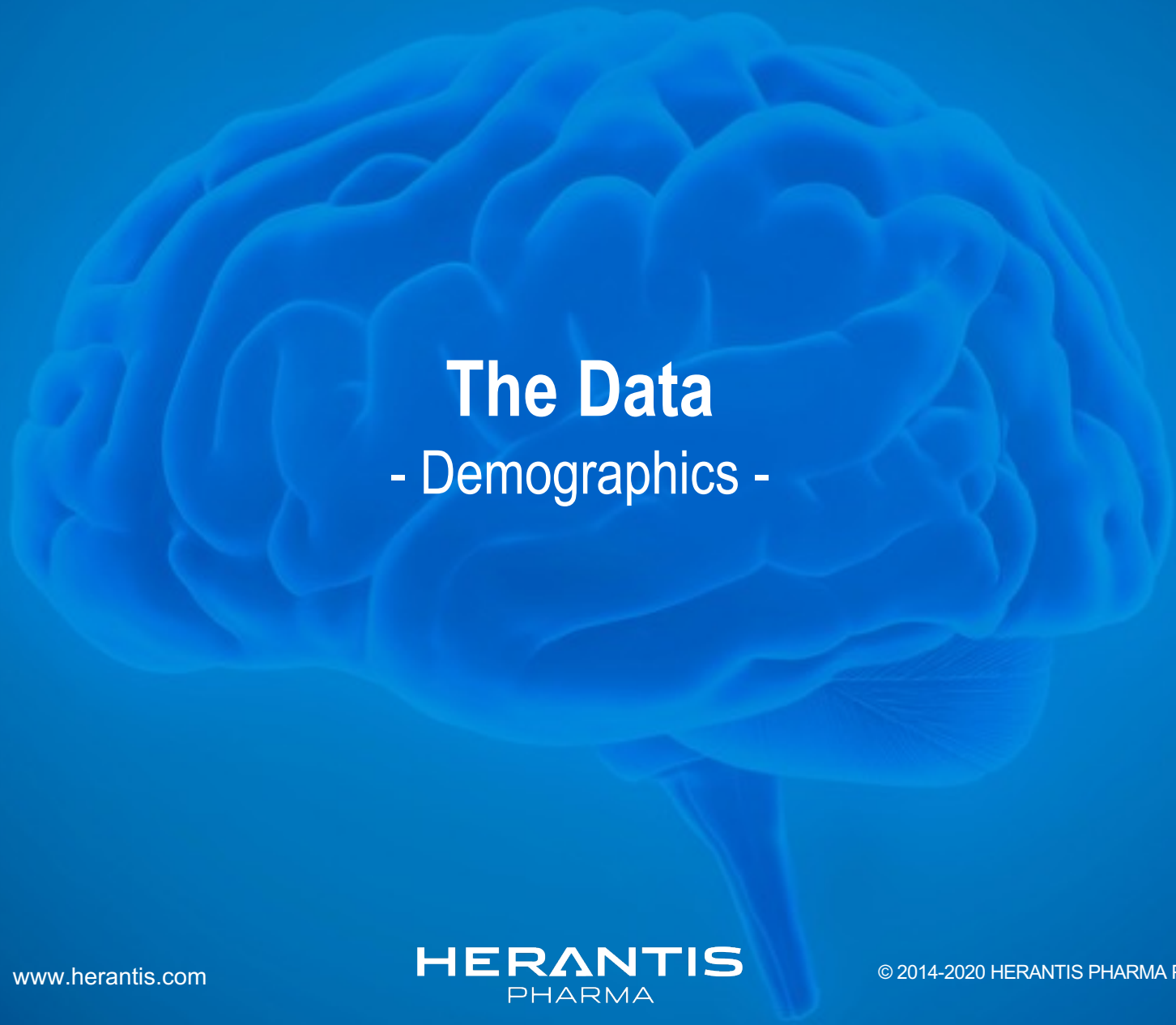
Endpoints (Drug-related)

- Primary endpoint
  - Safety (drug and device)
- Secondary endpoints
  - UPDRS Part III motor scores - severity of motor symptoms
  - TUG test - mobility
  - UPDRS Part I-IV total scores ON & OFF state - severity non-motor & motor symptoms
  - Home diary score - functional status
  - PDQ-39 score - health and daily activity
  - CGI scale - mental status
- Exploratory endpoints
  - DAT PET imaging - dopamine in caudate and putamen; integrity of nigrostriatal system
  - α-synuclein in serum and cerebrospinal fluid - biomarker
  - CDNF level - in CSF and serum
  - Proteomic biomarker screen - in CSF
  - Genome testing (NGS) - in saliva
  - Parkinson's KinetiGraph (PKG) Data Logger - daily activity measurement and changes



The Data

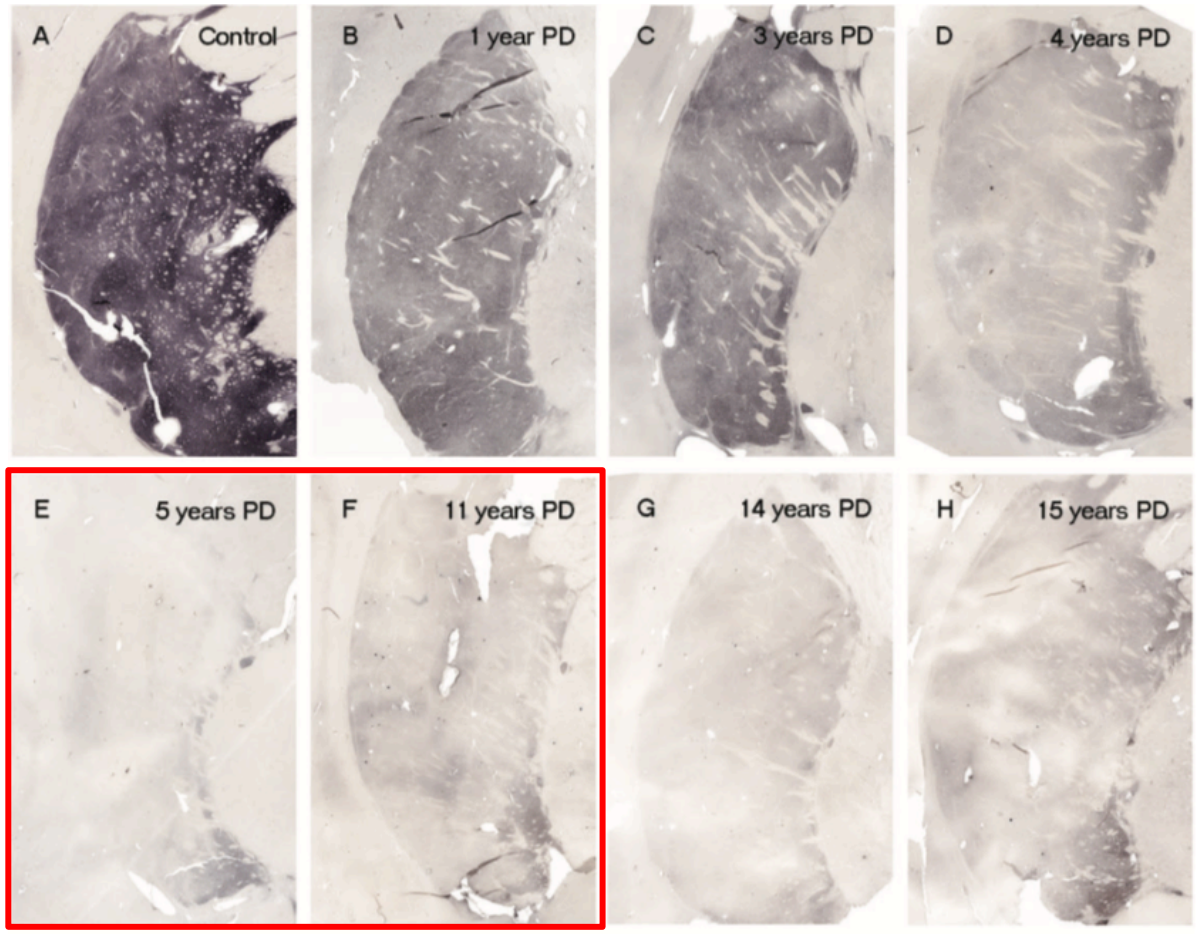
- Demographics -

Demographic and PD Characteristic Data At Screening

Characteristic	Placebo n=6	CDNF (low-mid-mid) n=6	CDNF (low-mid-high) n=5
Age (years)	63.8 ± 6.4	63.2 ± 8.9	57.8 ± 6.7
Male sex, n (%)	5 (83.3%)	3 (50%)	4 (80%)
White race, n (%)	6 (100%)	6 (100%)	5 (100%)
Hoehn & Yahr (OFF), n (%)			
Stage 2	4 (66.7%)	3 (50%)	2 (40%)
Stage 2.5	1 (16.7%)	1 (16.7%)	2 (40%)
Stage 3	1 (16.7%)	2 (33.3%)	1 (20%)
Disease duration since first motor symptoms (years)	10.5 ± 2.7	10.7 ± 3.1	10.8 ± 2.3
UPDRS III, OFF	33.3 ± 7.6	34.7 ± 7.3	31.0 ± 6.8
UPDRS III, ON	14.8 ± 6.9	14.3 ± 4.5	11.8 ± 7.1
Levodopa response, %	60.7 ± 13.9	57.6 ± 11.8	57.0 ± 20.4
OFF-time per day, h	4.7 ± 0.7	6.1 ± 1.5	4.4 ± 1.5

Safety Study Only, Not Efficacy – Here's Why

Dopamine transporter (DAT) staining



Kordower et al. Brain 136: 2419-31, 2013

- By 5 years post-diagnosis, the putamen is nearly completely devoid of DAT-positive dopaminergic neuron terminals
- The target of CDNF, the stressed and degenerating dopamine neurons and their terminals, are nearly completely lost from the target infusion area → it is unlikely to see significant clinical improvement
- Use of this patient group in the study was required by regulators and ethics committees

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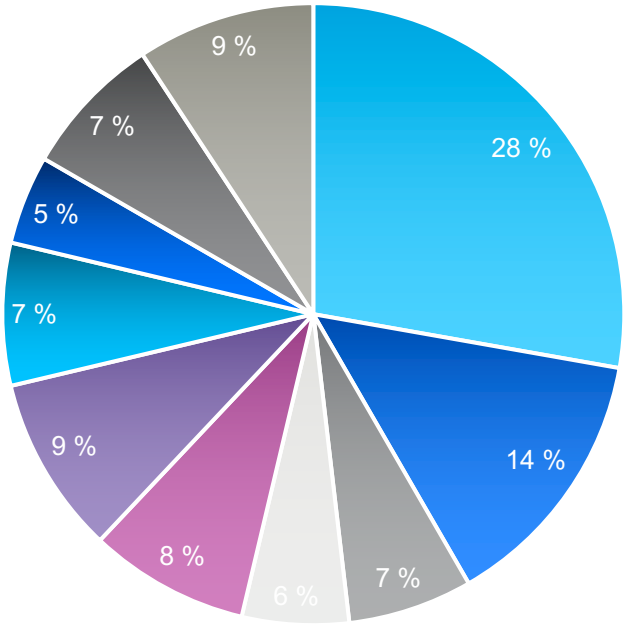
The Data

- Safety -

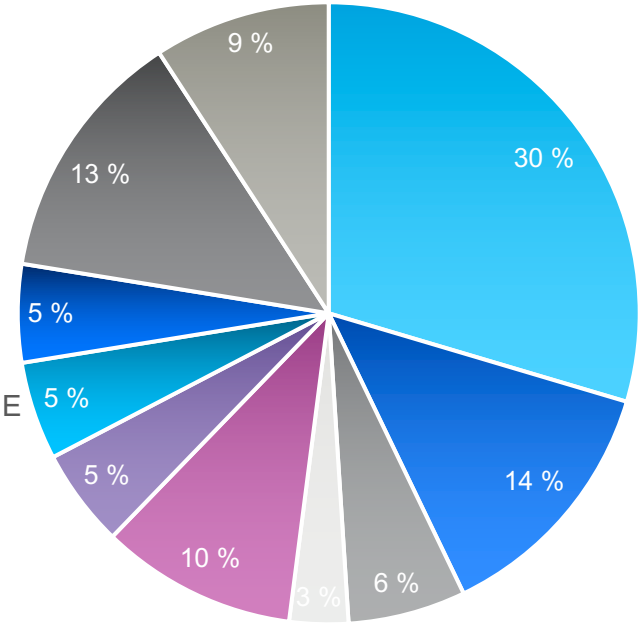
Treatment Emergent Adverse Events* Transient And Mild

0 – 6 month Main Study



- NERVOUS SYSTEM DISORDERS
- GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS
- PSYCHIATRIC DISORDERS
- INJURY, POISONING AND PROCEDURAL COMPLICATIONS
- INFECTIONS AND INFESTATIONS
- GASTROINTESTINAL DISORDERS
- MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS
- SKIN AND SUBCUTANEOUS TISSUE DISORDERS
- INVESTIGATIONS (BLOOD AND URINE TESTING)
- OTHER

6 - 12 month Extension Study



* Includes all adverse events after first treatment dosing; both related and unrelated to treatment

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Treatment Related Serious Adverse Events Resolved

Infectious events:

- Brain abscess occured in Main study during the first 6-month period
- Port skin necrosis in Main study during the first 6-month period

Risk mitigation improvements made to surgical procedure, infusion procedure, device maintenance procedure, and additional training of investigators

After risk mitigation improvements, 87 infusions conducted without infusion procedure-related infections or other AEs

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Primary Endpoint Of The Study Was Met

- ☑ Majority of the reported drug-related TEAEs were mild and have recovered
- ☑ Similar safety profile in Main (0 – 6 months) and Extension (6 – 12 months) study
- ☑ Similar safety profile between dose-groups
- ☑ SAE's related to device, improvements made to use and preparation
- ☑ No dose-limiting toxicities related to CDNF

The Data

- Efficacy –

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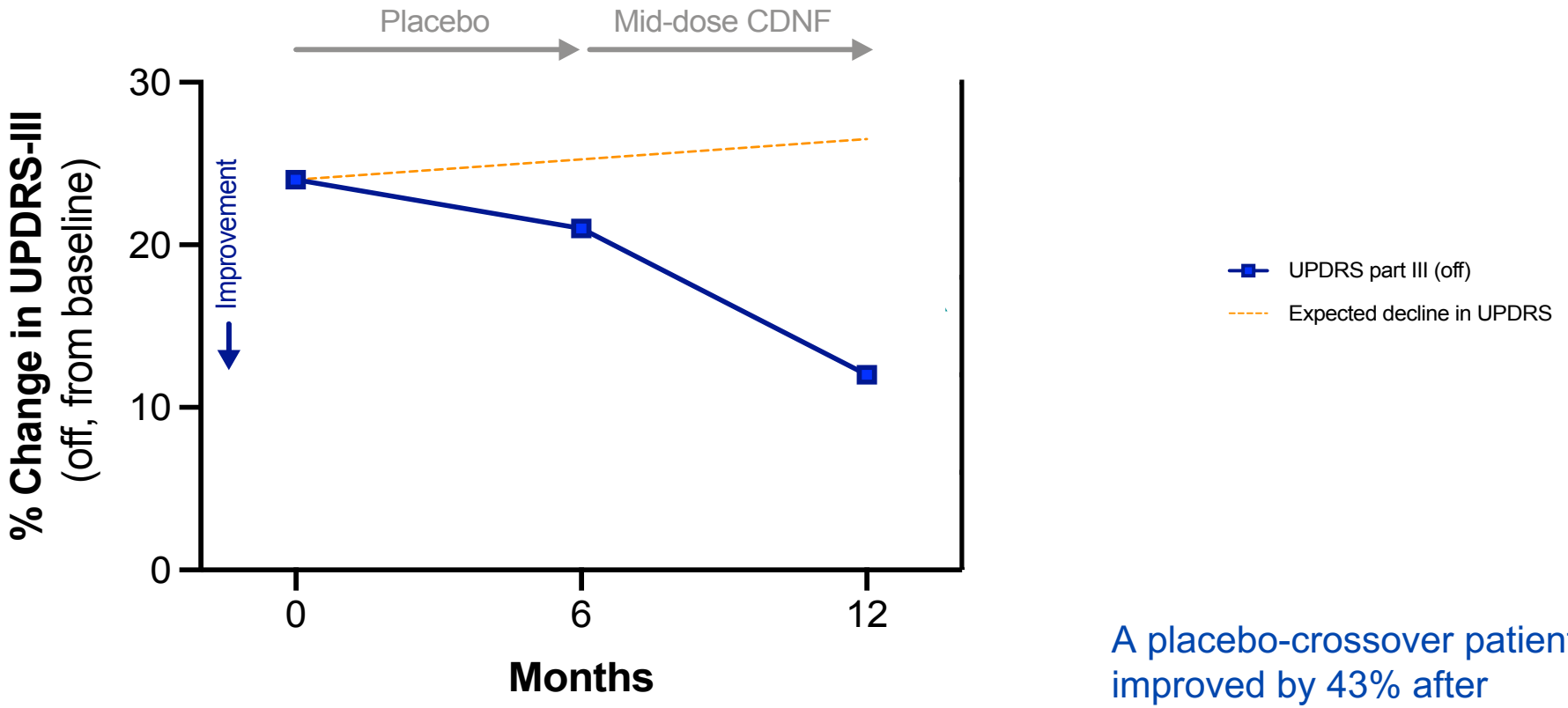
UPDRS Part III and Home Diary Explained

- UPDRS Total (Parts I-IV):
  - Rating tool used to gauge the course of movement hindrances of PD patients
  - Five segments including mentation, behaviour, mood, ADL, motor sections
  - Grades assigned to each extremity:
    - → possible maximum of 199 points worst total disability, a score of zero represents no disability
    - → comprehensive, but variable tool hence use needs appropriate statistical power to minimise 'noise'
  - Part III (off medication) evaluates motor function:
    - → speech, expression, tremor, rigidity, finger taps, rapid hand movements, leg agility, etc
    - → **PD patients typically worsen by 2 to 2.5 points per year**
- Home Diary: Patients report motor state for every half hour over a three day period:
  - → ON, ON with non-troublesome dyskinesias, ON with troublesome dyskinesias, OFF and asleep
    - "bad time" : OFF time and ON time with troublesome dyskinesias
    - "good time" : ON time and ON time with non-troublesome dyskinesias
  - → Considered potential more realistic than UPDRS (scored by physician)

Some Impressive Individual Cases



A placebo-crossover patient improved by 43% after receiving 6 doses of CDNF

- The patient received six placebo infusions (Main study), followed by re-randomization and two low-doses (120 μg) and four mid-doses of CDNF (400 μg) in the Extension study

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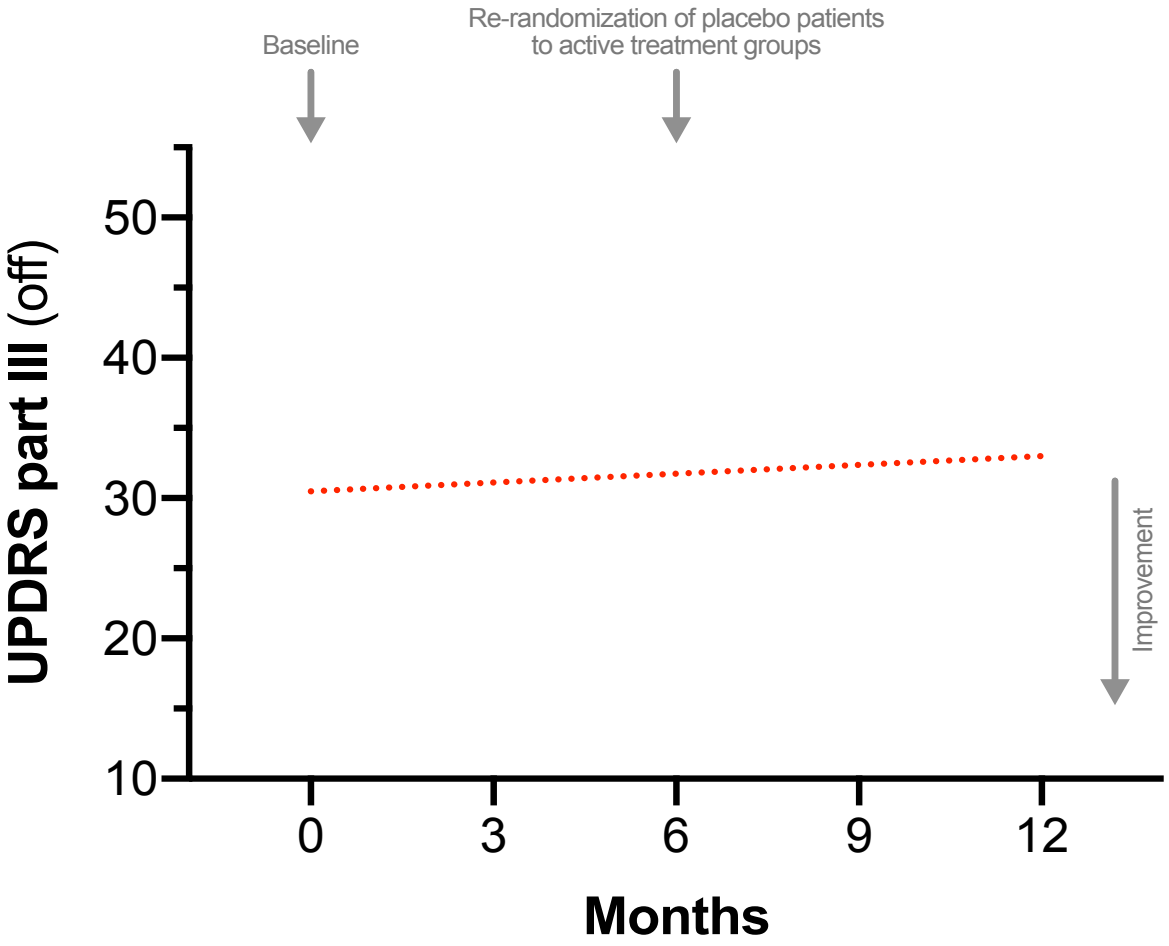
UPDRS Part III (off) Absolute Scores

What We Would Expect in Parkinsons Patients



Expected annual decline

PD patients typically worsen by 2 to 2.5 points per year

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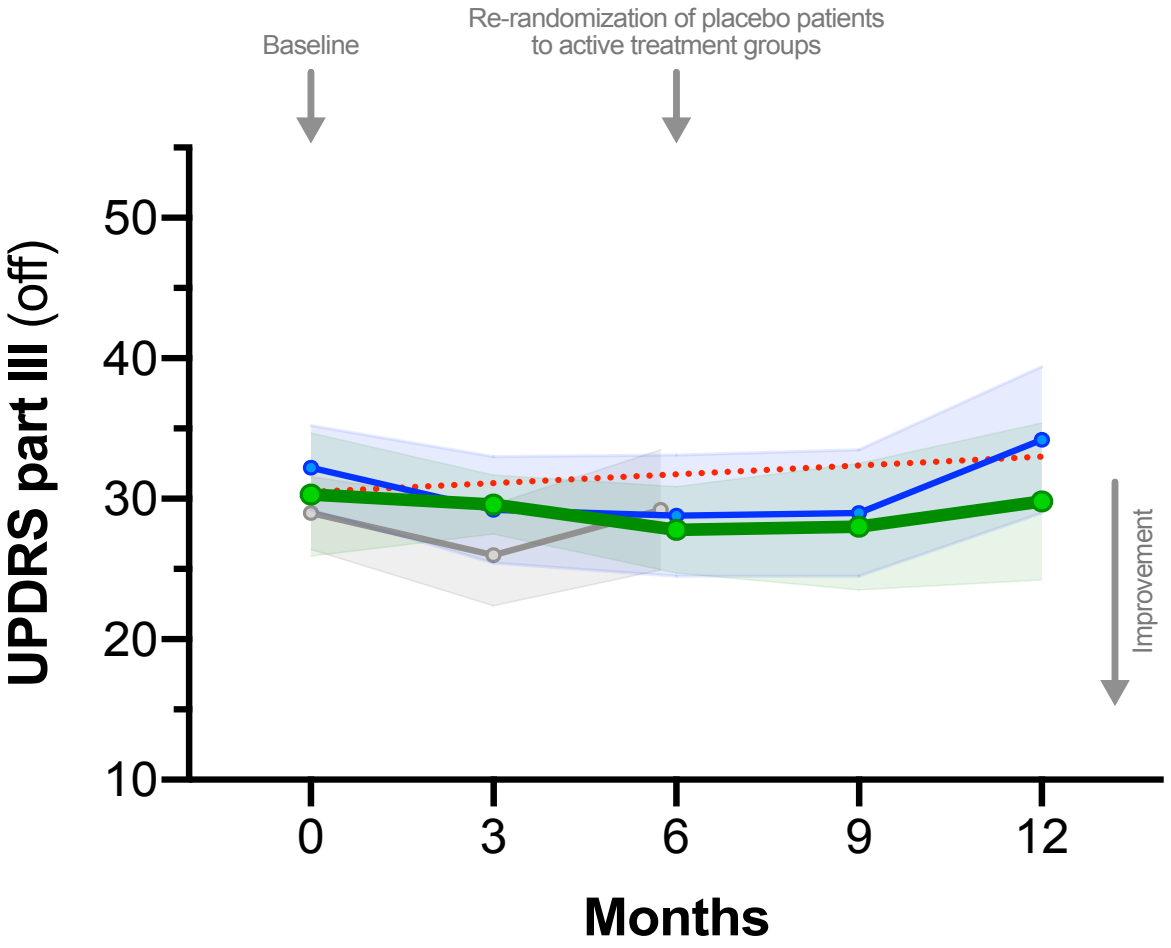
UPDRS Part III (off) Absolute Scores

What We Actually Observed in Study Patients



All CDNF-treated patients: achieved definition of **'minimal clinically important difference'** in UPDRS part 3 (motor score); 1.4-2.6 point improvement (pooled data)

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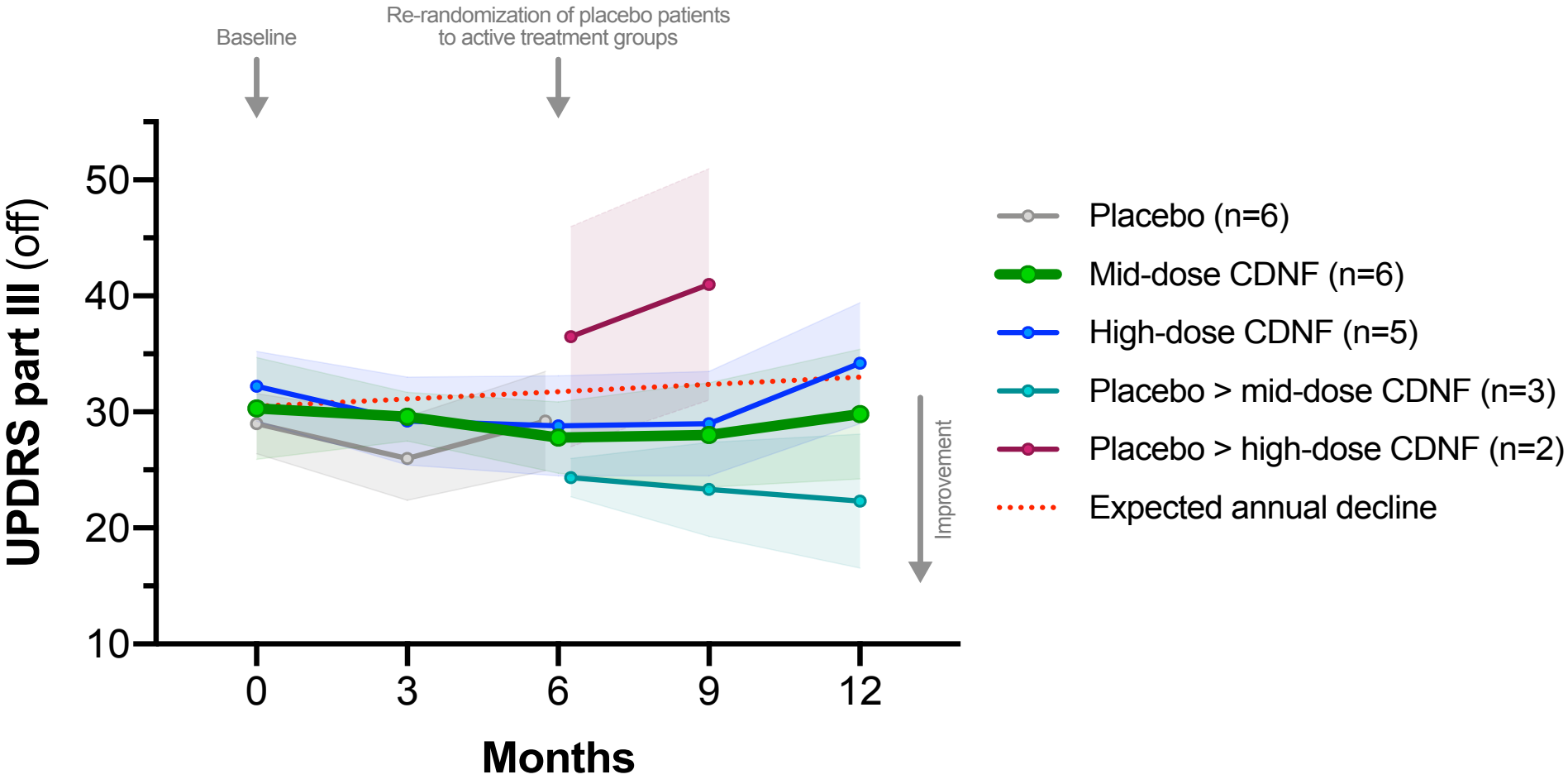
UPDRS Part III (off) Absolute Scores

What We Actually Observed in Study Patients



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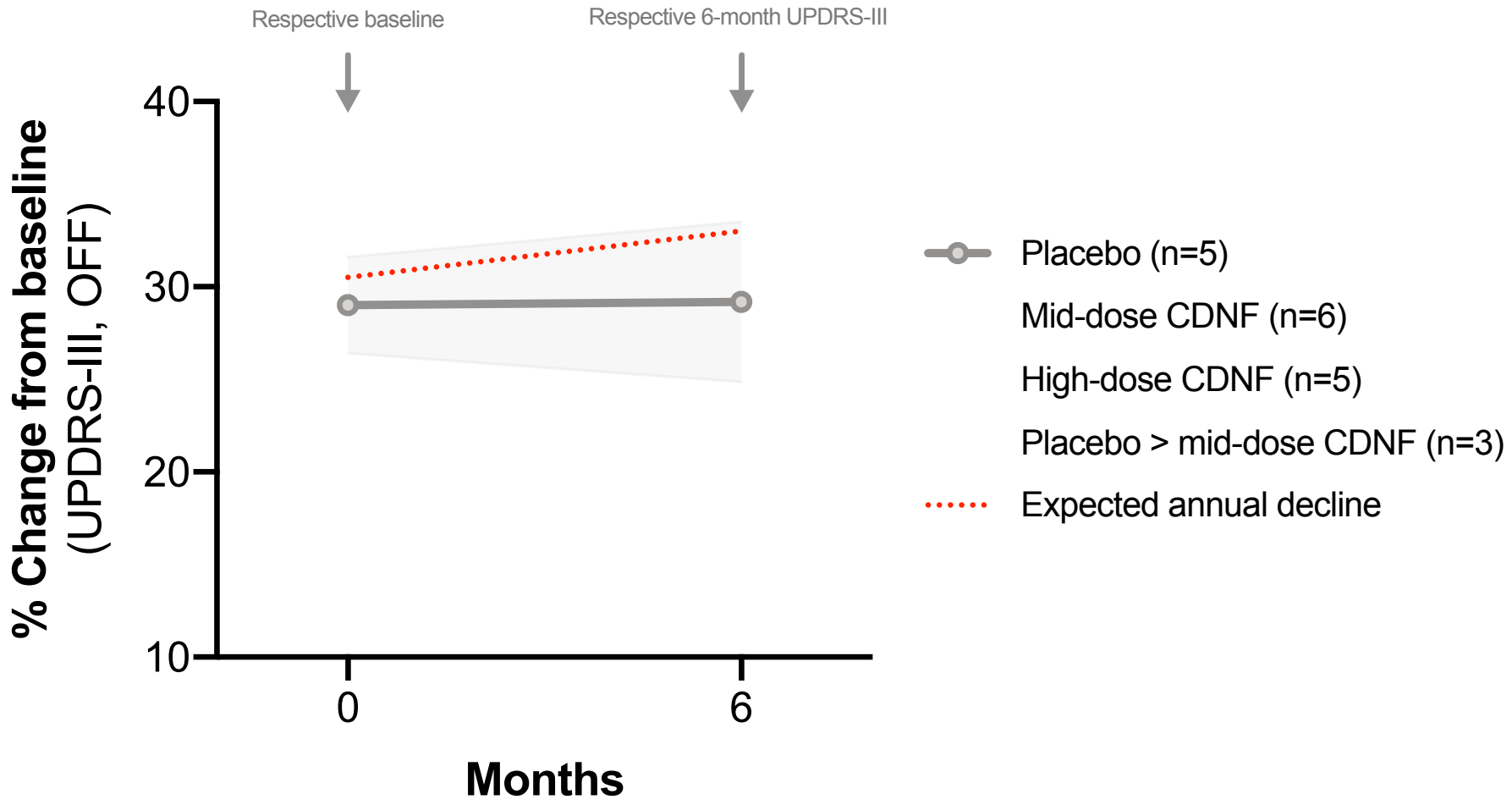
UPDRS-III (off) First 6-Month Treatment vs Placebo

What We Would Expect in Parkinsons Patients



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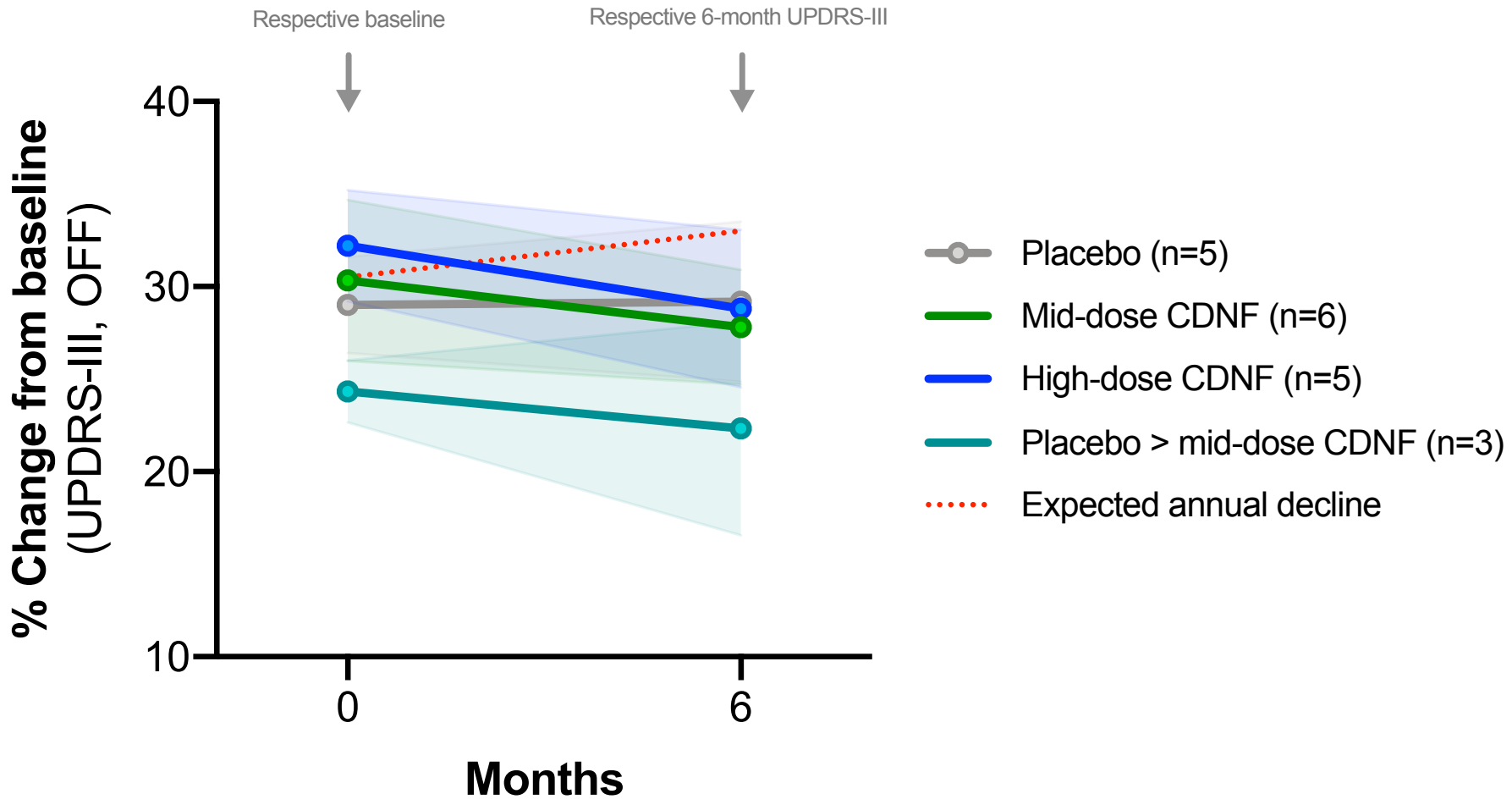
UPDRS-III (off) First 6-Month Treatment vs Placebo

What We Actually Observed in Study Patients



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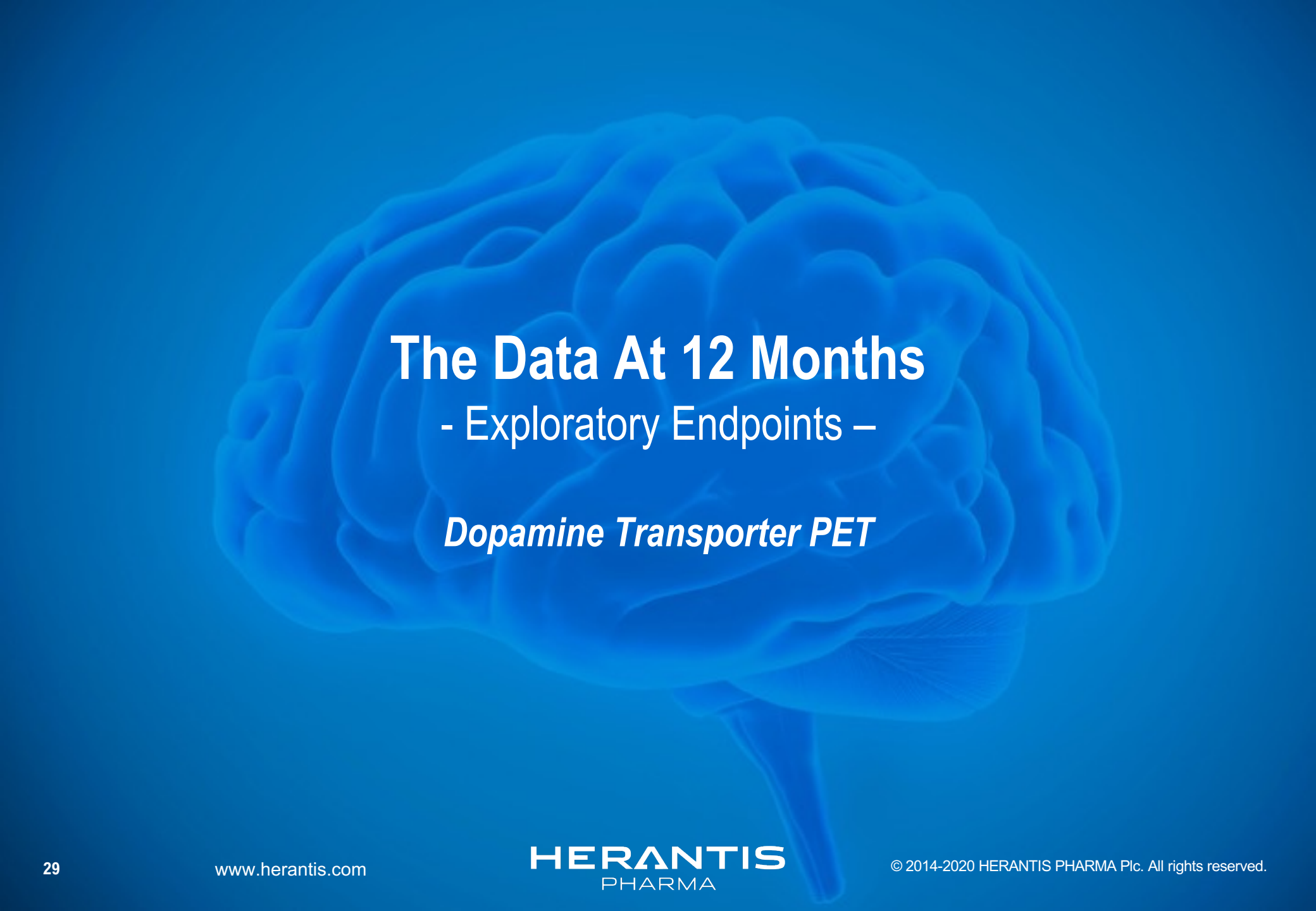

The Data At 12 Months

- Exploratory Endpoints –

Dopamine Transporter PET

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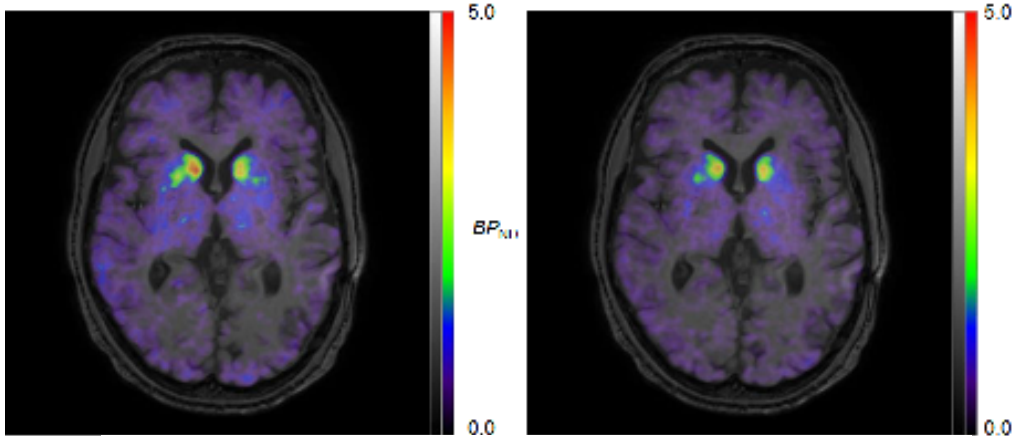
Exploratory Endpoint Dopamine Transporter DAT Explained

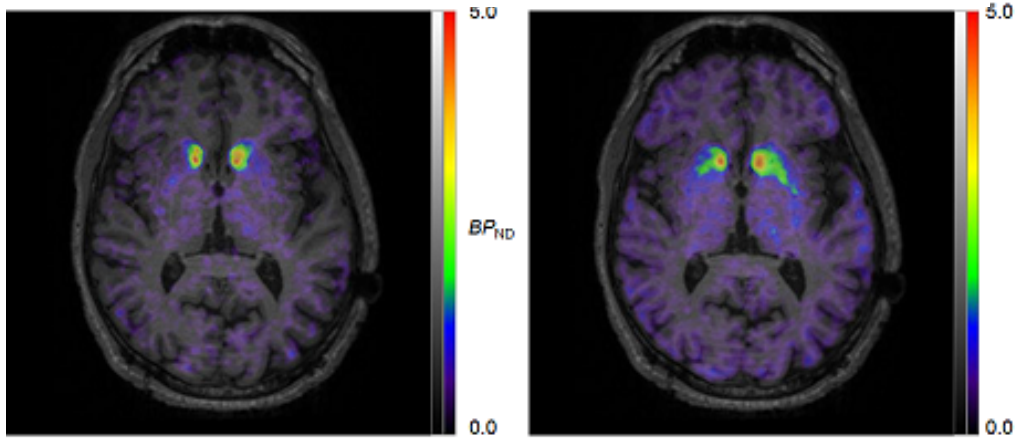
- Marker of integrity and density of dopamine neurons and terminals
- Visualization of loss of striatal dopaminergic nerve endings correlates with motor symptoms and disease stage
- Annual rate of reduction of striatal DAT PET signal in PD patients is 6-13% compared to 0-2.5% in healthy, age-matched controls
- DAT PET scans were performed at 0, 6, 12, 19 months with [^{18}F]FE-PE2I tracer
- All Swedish patients were imaged at Karolinska Hospital PET Center and all Finnish patients at Turku PET Center

Example of decreased signal: patient on placebo



Baseline 6 months

Example of increased signal: patient on mid-dose CDNF



Baseline 6 months

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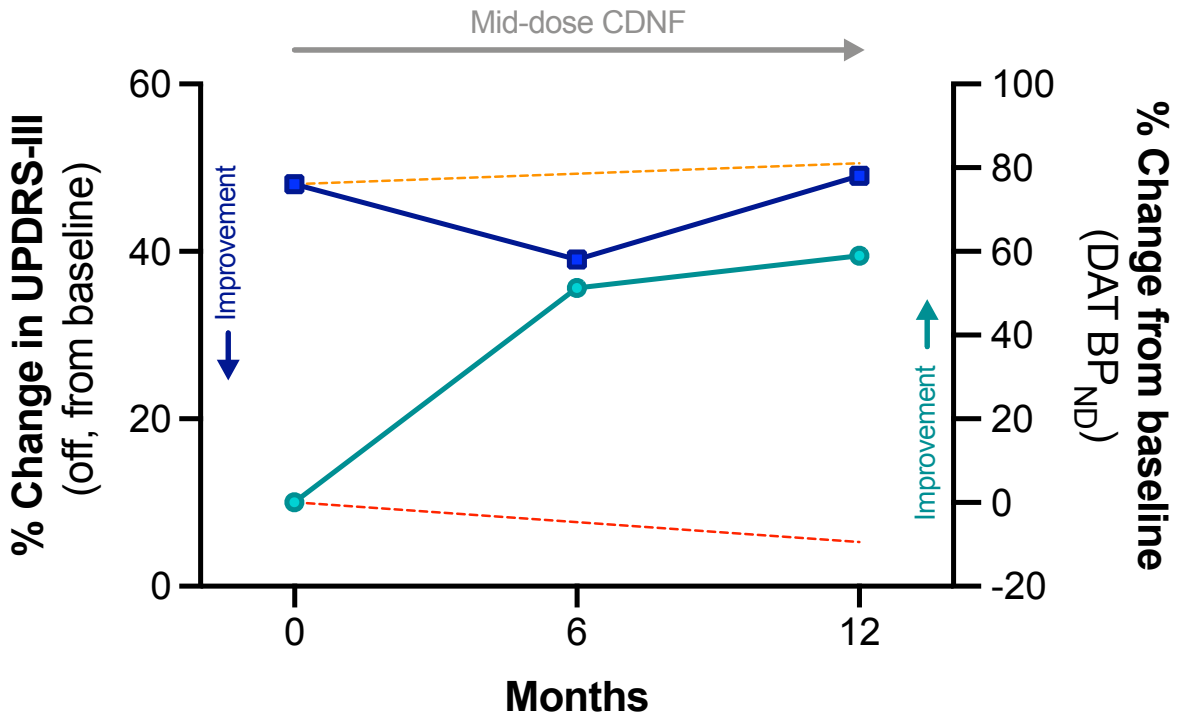
Some Impressive Individual PET Cases



UPDRS part III (off)

Expected decline in UPDRS

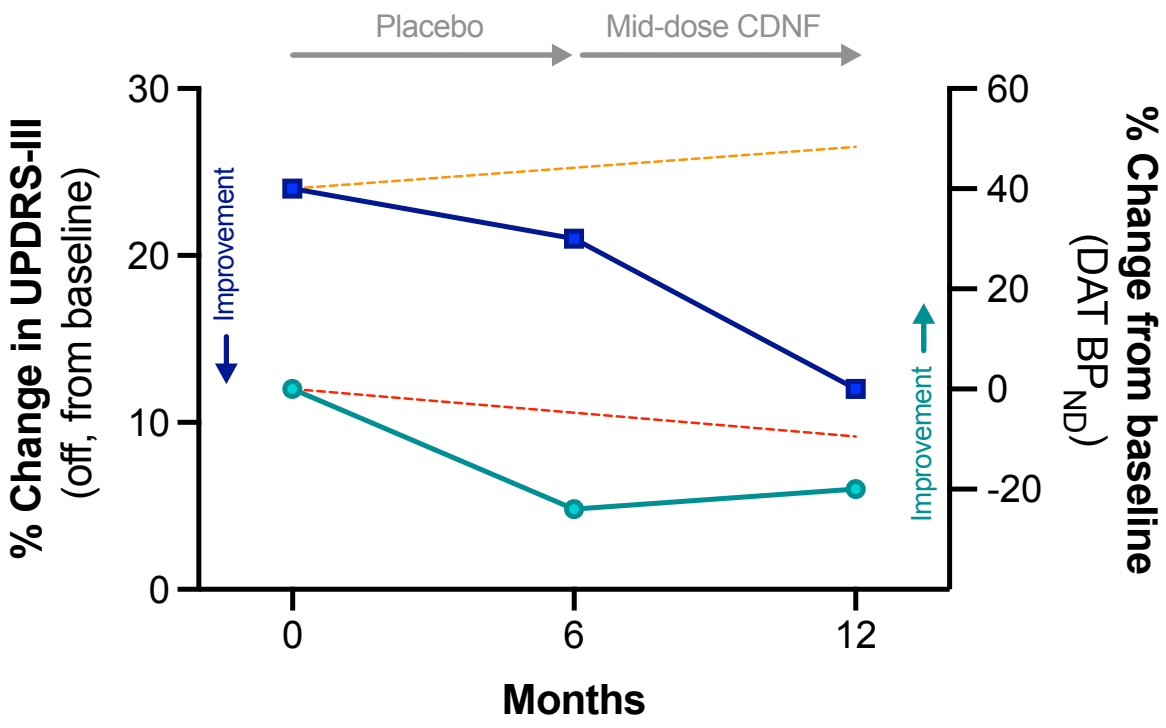
DAT PET

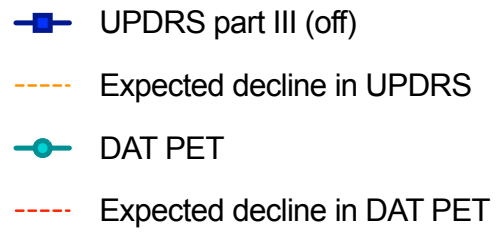
Expected decline in DAT PET

A mid-dose patient showed >50% gain in PET at 6 & 12 months

- The patient received two low-doses (120 μg) of CDNF and 10 mid-doses (400 μg) of CDNF over 12 months

Some Impressive Individual PET Cases





A patient who had crossed over from placebo to mid-dose CDNF improved in UPDRS by 43% over 12 months and had 5% increase in DAT PET

- The patient received six placebo infusions (Main study), followed by re-randomization and two low-doses (120 μg) and four mid-doses of CDNF (400 μg) in the Extension study

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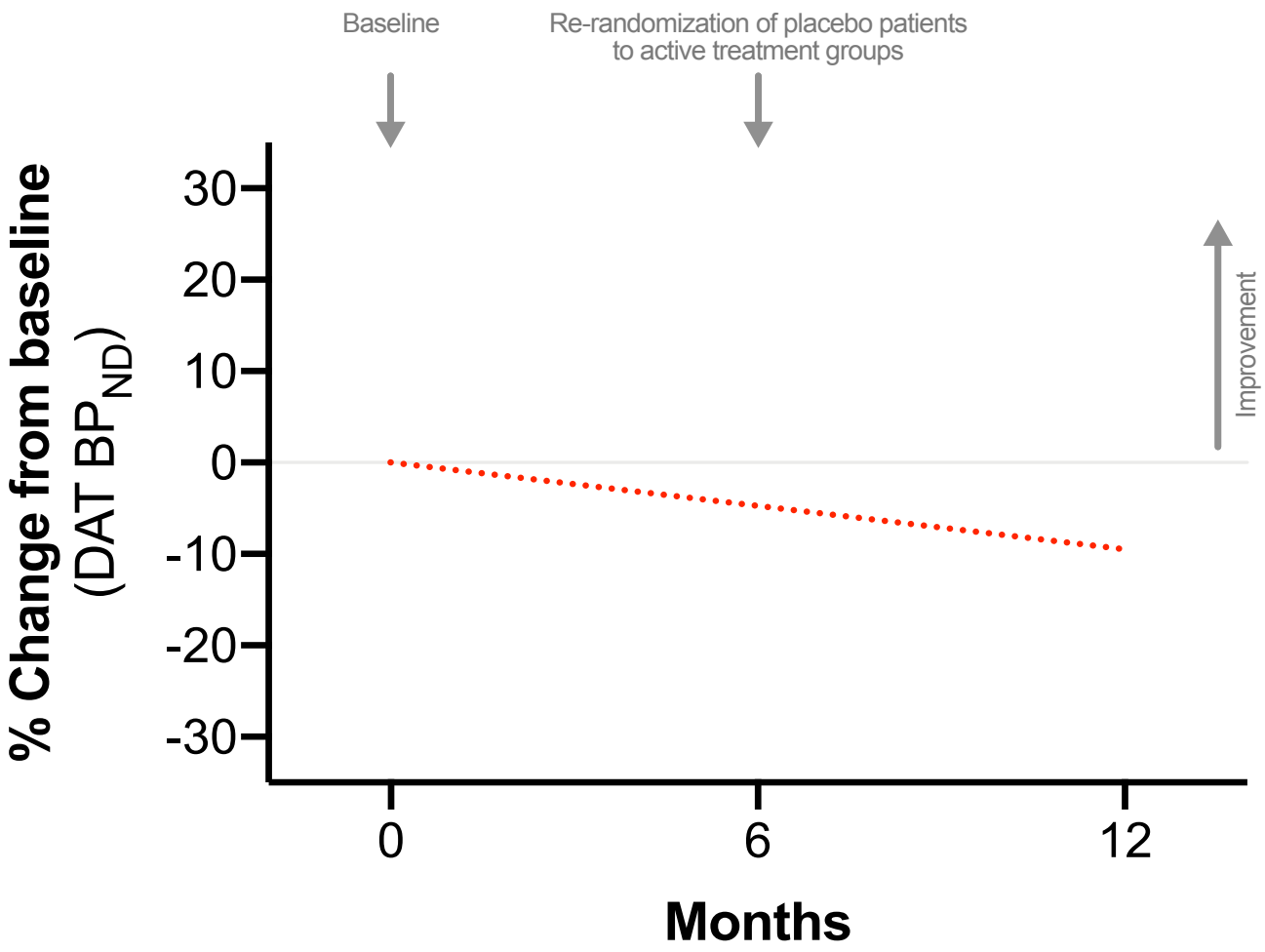
DAT PET Responses Over 12 Months

What We Would Expect in Parkinsons Patients



Expected annual decline

PD patients' average annual decrease is 6-13%

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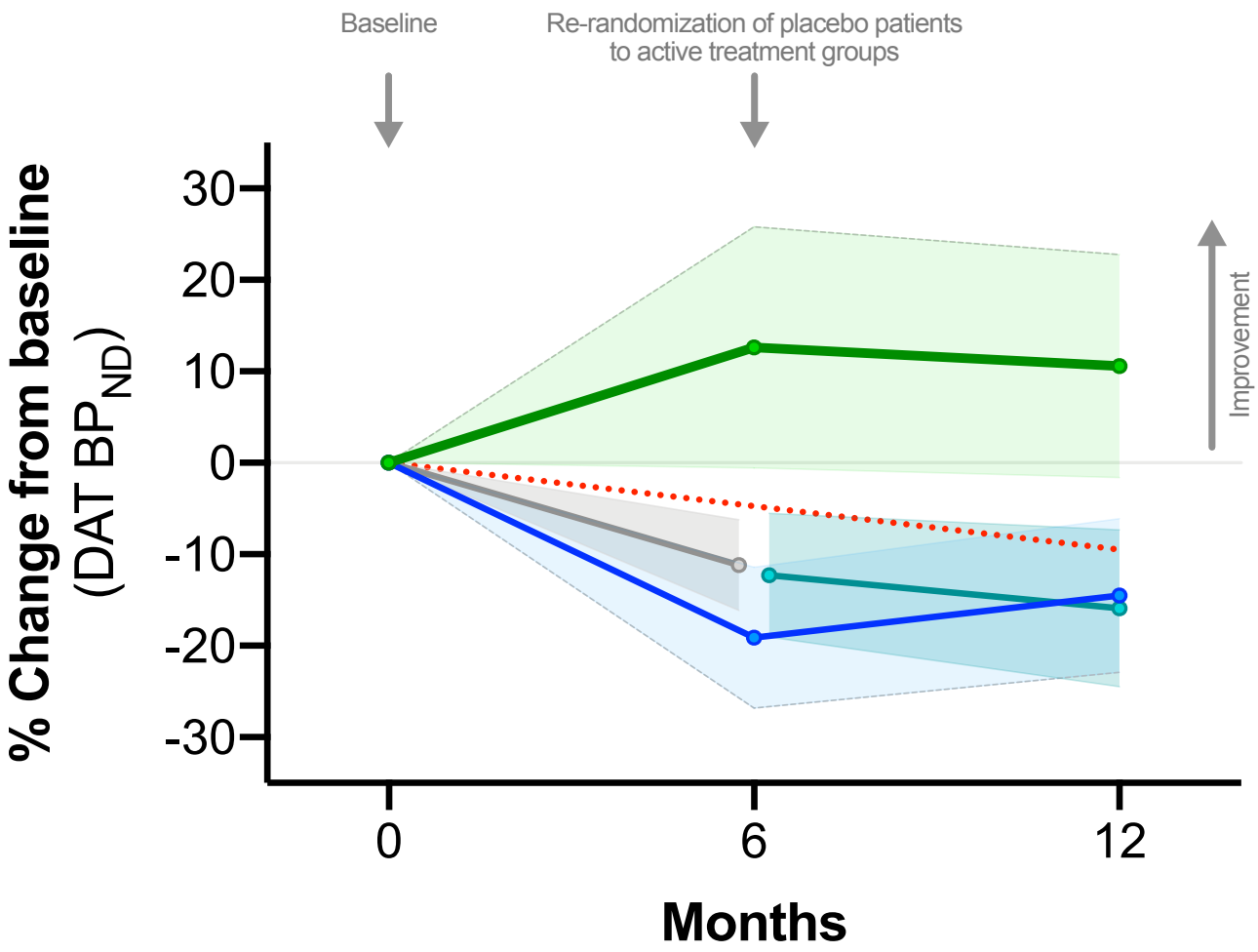
DAT PET Responses Over 12 Months

What We Actually Observed in Study Patients



- Placebo (n=6)
- Mid-dose CDNF (n=6)
- High-dose CDNF (n=5)
- Placebo > mid-dose CDNF
- Expected annual decline

Increase in average DAT binding potential in mid-dose CDNF group (+15%)

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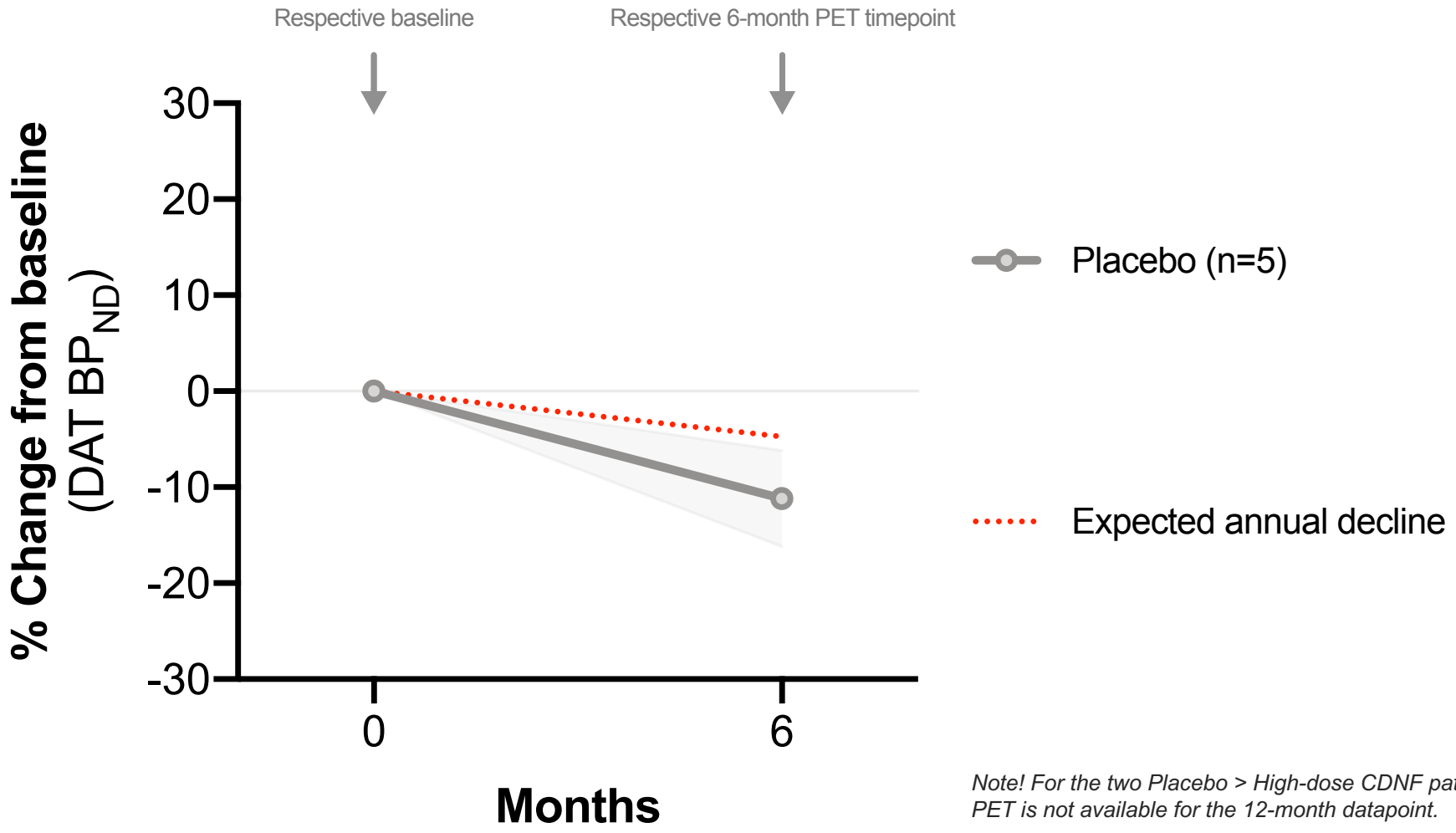
DAT PET Response First 6-Month Treatment vs Placebo

What We Would Expect in Parkinsons Patients



Note! For the two Placebo > High-dose CDNF patients, PET is not available for the 12-month datapoint.

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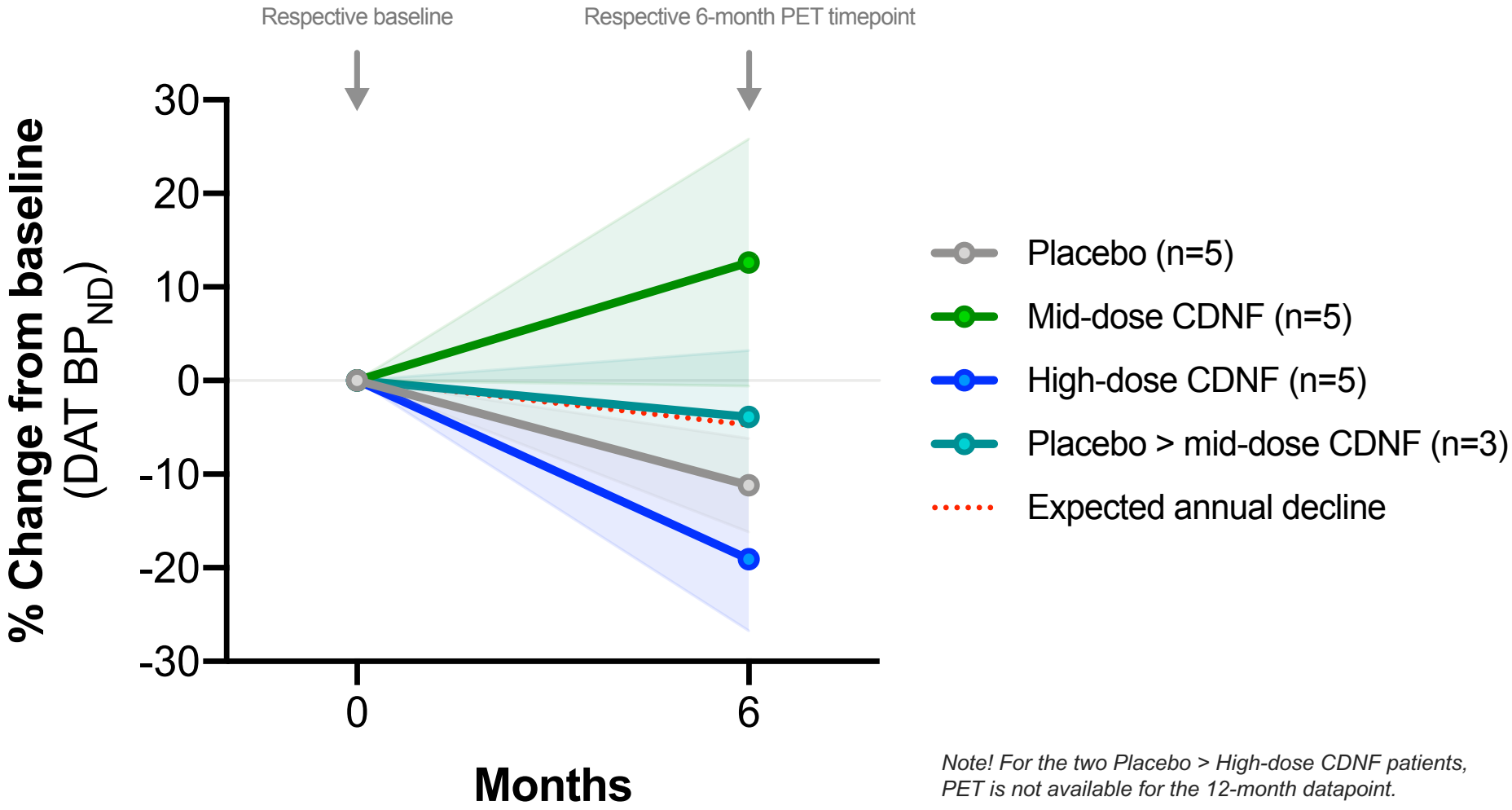
DAT PET Response First 6-Month Treatment vs Placebo

What We Actually Observed in Study Patients



Note! For the two Placebo > High-dose CDNF patients, PET is not available for the 12-month datapoint.

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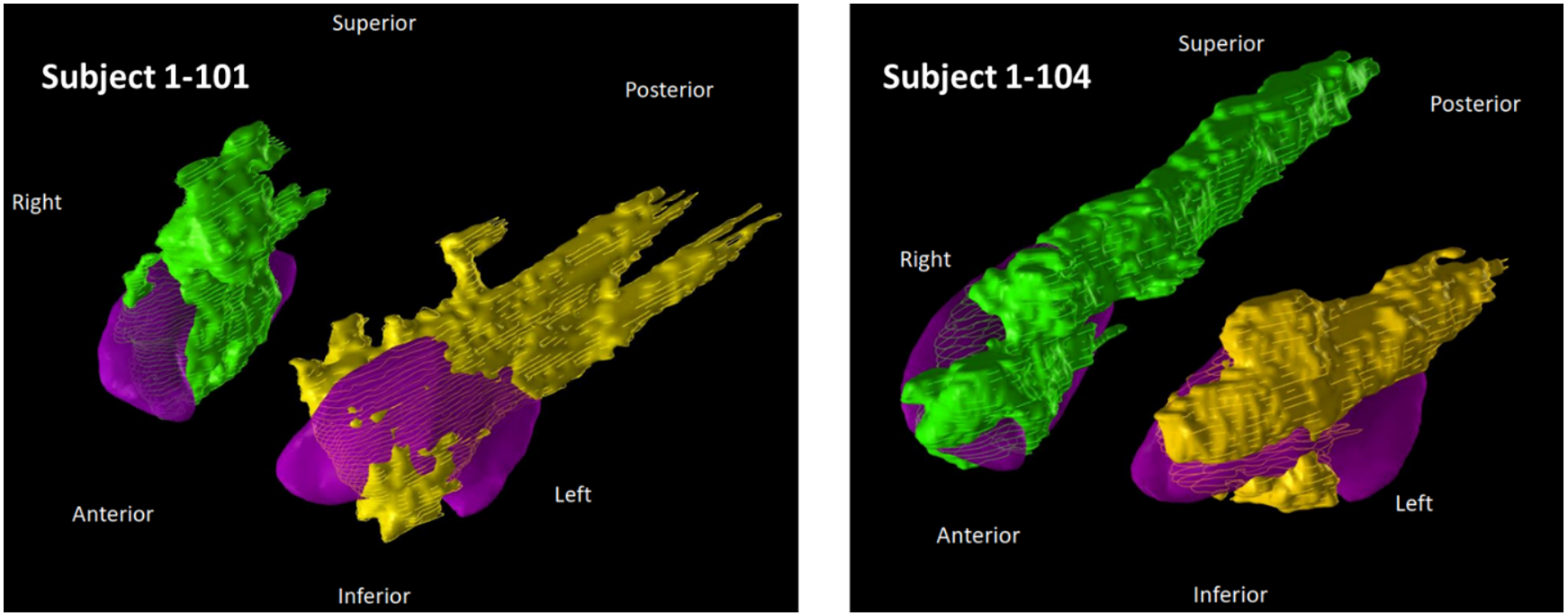
Good CDNF Infusate Coverage Achieved In The Putamen

- Quantitative MRI analysis of contrast agent distribution showed **60-75% coverage** of the putamen volume
- Gadolinium contrast agent test infusions were carried only for the two first patients.



The lines shown within the putamen indicate the infusate distribution position within structure.
Colour codes: purple: putamen; green: infusate in right side; yellow: infusate in left side.

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Conclusions & Next Steps

Key Conclusions

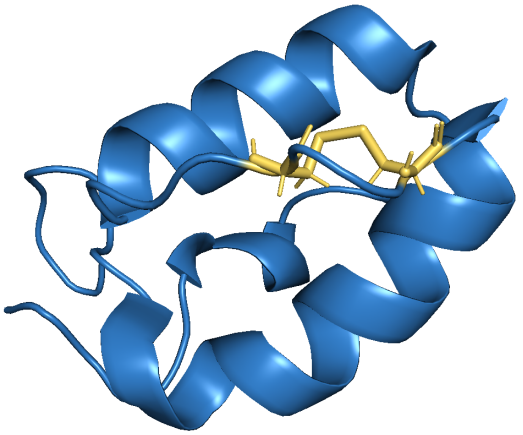
- From safety perspective
  - CDNF drug safety established
  - Study procedures improved for future studies
- From efficacy perspective
  - Not possible to gauge efficacy in this group of patients – a lot of ‘noise’ due to:
    - Disease severity (CDNF dopamine target already lost hence nothing to act on)
    - Small unpowered study numbers
- Despite the difficult patient group, some encouraging observations
  - No worsening of disease
  - Some suggestions of improved biological signals in some patients
  - Some interesting individual cases
- Our understanding of CDNF and treatment of Parkinson’s disease has advanced massively with this study

Moving Forward

- Shape program moving forward to maximise chances of success and partnerability
- Finalise outstanding data on alpha-synuclein, proteomics, CSF
- Key areas of focus
  - Earlier disease patients where dopaminergic neurons are still present
  - Adequately powered study with sufficient patient numbers
  - Optimise dosing
- Continue to explore indications beyond PD such as stroke
- xCDNF
  - Prepare for full xCDNF pre-clinical program pending lead compound selection

CDNF Results Compelling Platform For Next Gen xCDNF

- Common challenge in CNS diseases is drug delivery to the brain (as noted in this study)
  - CDNF currently administered via surgically implanted device
- xCDNF, i.e. smaller selected fragments of CDNF
  - retain the biological activity of CDNF
  - penetrate the BBB
  - highly potent molecules
  - engineered for improved metabolic stability



- xCDNF at final stages of compound selection to take forward into development
  - will not require surgical device
  - administration via simple peripheral injection
- Potential indications in several neurodegenerative diseases

Thank You

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