



Attacks Alzheimer's Disease and
Neurodegeneration by Improving the
Information Highway of the Nerve Cell

Axonal Transport

Symbol: **ANVS** (NYSE)

January 2022



FORWARD-LOOKING STATEMENTS

Statements in this presentation contain “forward-looking statements” that are subject to substantial risks and uncertainties. Forward-looking statements contained in this presentation may be identified by the use of words such as “anticipate,” “expect,” “believe,” “will,” “may,” “should,” “estimate,” “project,” “outlook,” “forecast” or other similar words, and include, without limitation, statements regarding Annovis Bio, Inc.’s expectations regarding projected timelines of clinical trials, and expectations regarding current or future clinical trials. Forward-looking statements are based on Annovis Bio, Inc.’s current expectations and are subject to inherent uncertainties, risks and assumptions that are difficult to predict. Further, certain forward-looking statements are based on assumptions as to future events that may not prove to be accurate, including that clinical trials may be delayed; that the data reported herein is from a Phase 2a study and subsequent clinical trials must be conducted; and that any anticipated meeting with or presentation to the FDA may be delayed. These and other risks and uncertainties are described more fully in the section titled “Risk Factors” in the Annual Report on Form 10-K for the year ended December 31, 2020 and other reports filed with the Securities and Exchange Commission. Forward-looking statements contained in this presentation are made as of this date, and Annovis Bio, Inc. undertakes no duty to update such information except as required under applicable law.

HIGHLIGHTS

A novel approach to treat neurodegenerative diseases is desperately needed

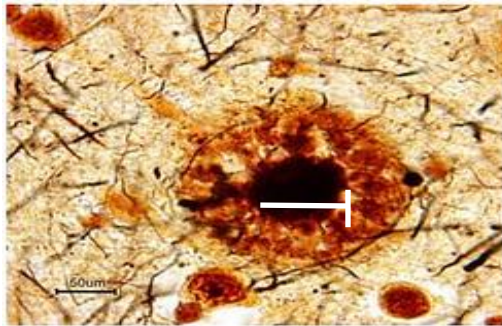
- **Annovis is developing drugs** for Alzheimer's (AD) and Parkinson's disease (PD)
- **Lead compound – Buntanetap (formerly known as ANVS401 or Posiphen) - in Phase 2a clinical trial**, is the only drug to improve cognition in AD and motor function in PD patients
- **Buntanetap restores the health of the nerve cell and improves function** in AD and PD patients
- **Successful completion of phase 2a clinical trials** has provided validation of our approach and allows us to plan for Phase 3 trials. We have asked the FDA for meetings.

ANNOVIS' NEW APPROACH TO ATTACK AD AND PD

Chronic and acute brain insults lead to high levels of neurotoxic proteins, inflammation and neurodegeneration

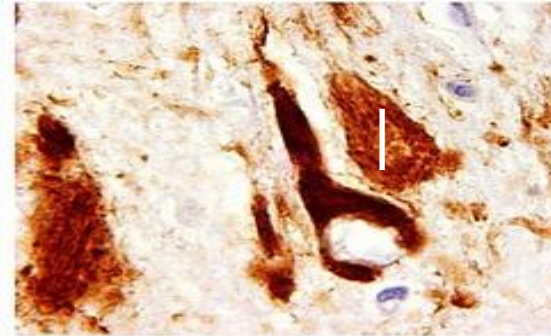
Amyloid β

Alzheimer's - Parkinson's
 $A\beta$ Targeting Compounds



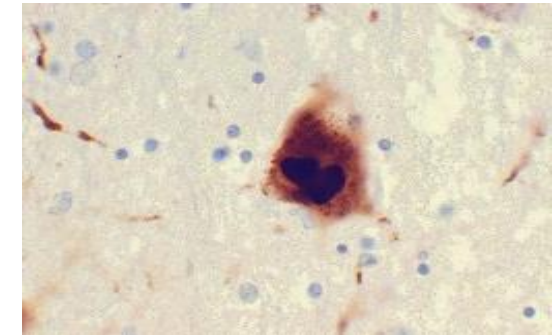
Tau

Tauopathies - Alzheimer's
Tau Targeting Compounds



α Synuclein

Parkinson's - Alzheimer's
 α SYN Targeting Compounds



Attacking one neurotoxic protein results in minimal effect

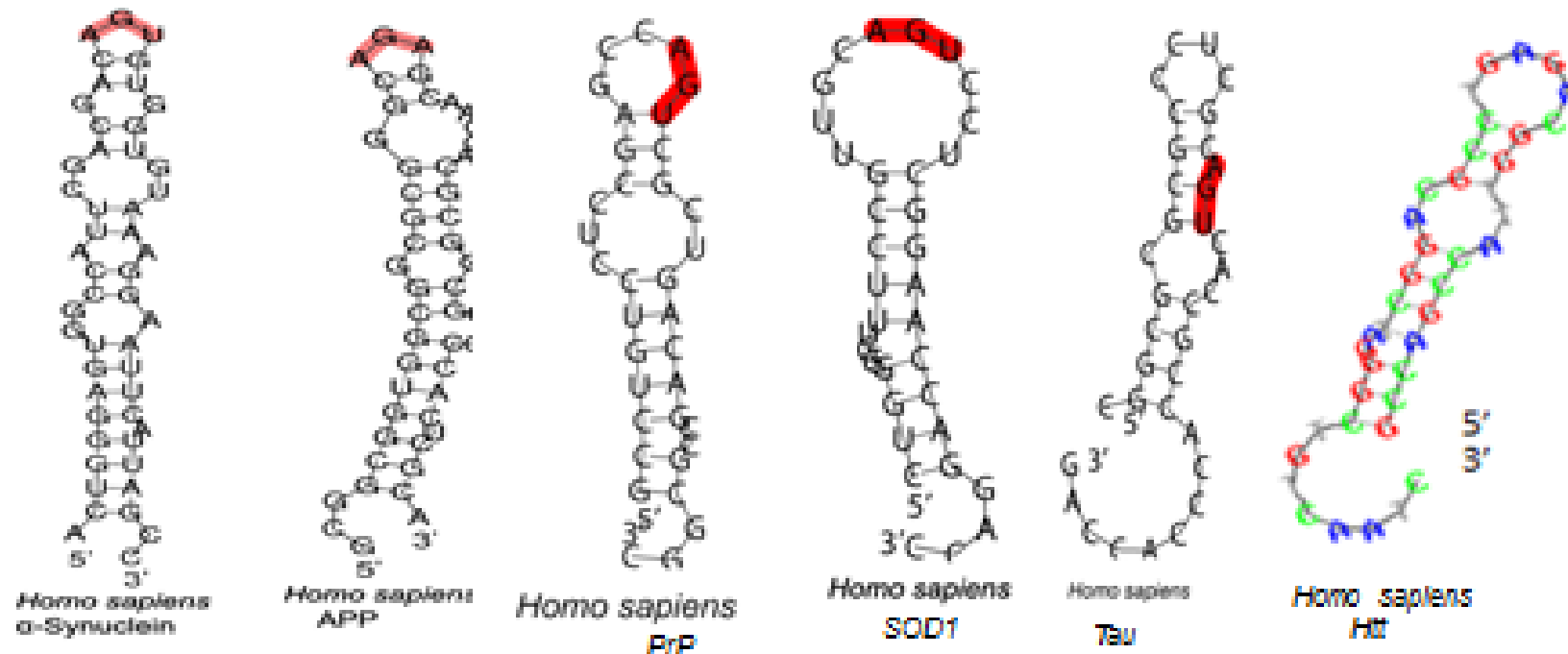
Buntanetap is the only drug to attack multiple neurotoxic proteins simultaneously

MECHANISM OF ACTION

Buntanetap is a translational inhibitor of neurotoxic aggregating proteins (TINAP)

5' UTR IRE Stem Loop Homology of Neurotoxic

Aggregating Protein mRNAs



Highly Preserved Consensus Loop in 5'UTR
>50% homology between 5'UTRs of mRNAs

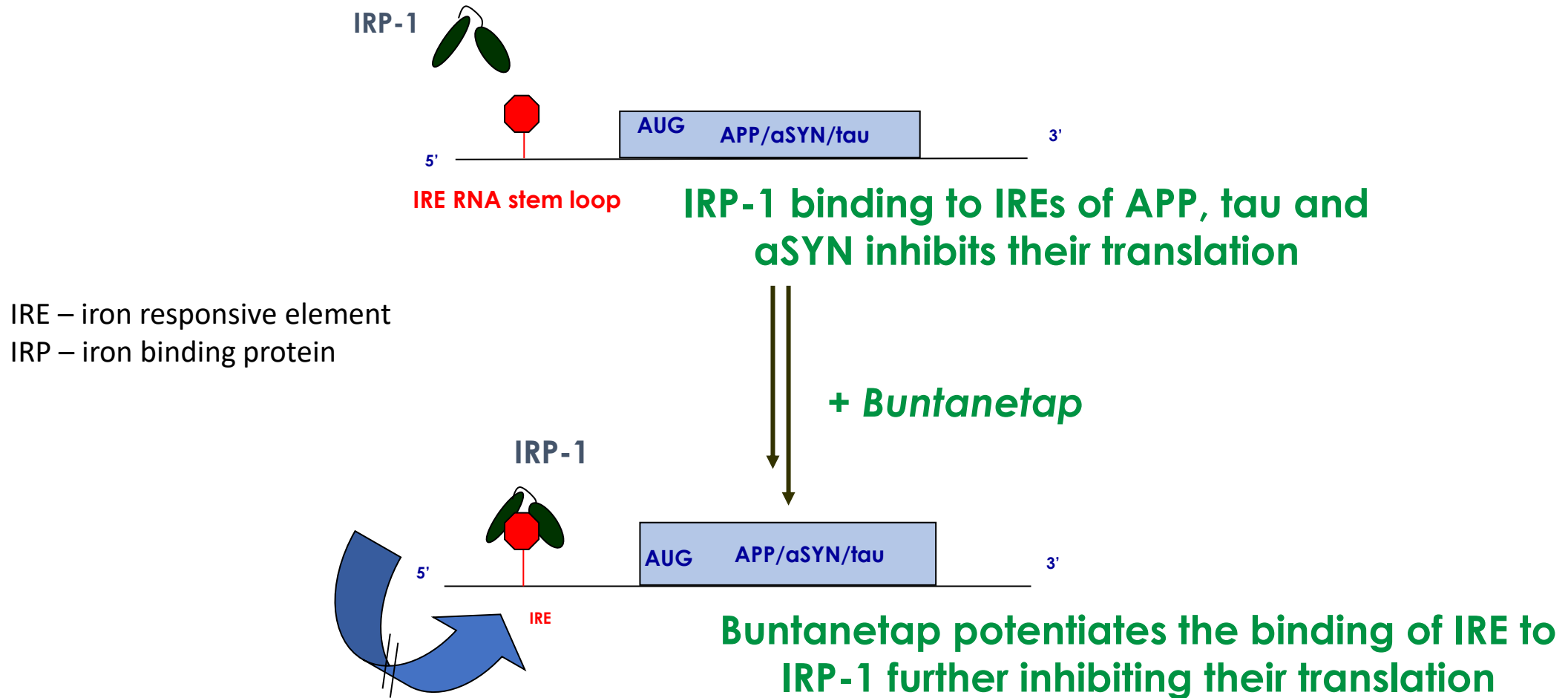
MECHANISM OF ACTION

Molecular Model of how Buntanetap locks IRP1 in the RNA Binding Position

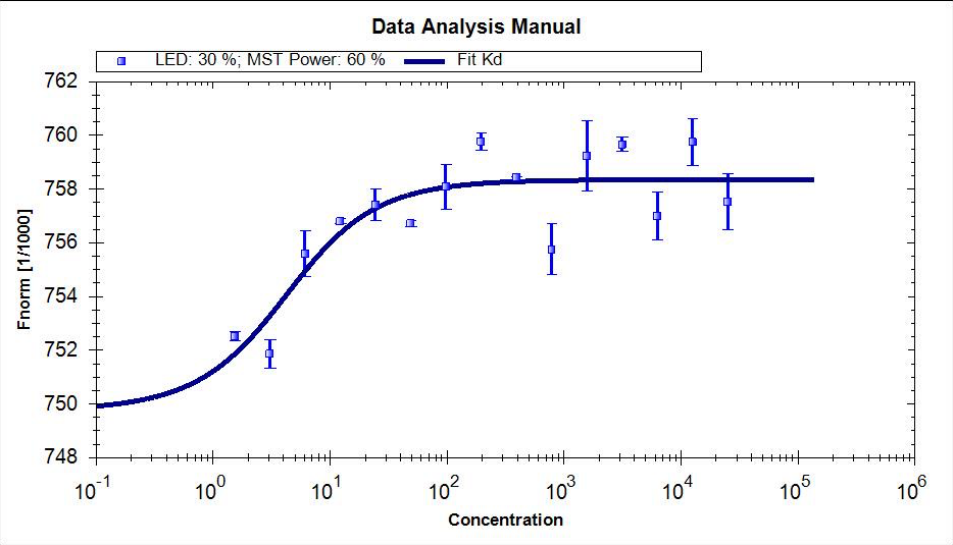


MECHANISM OF ACTION

Buntanetap potentiates the binding of IRE to IRP1



IRE to IRP1 BINDING IS SPECIFIC FOR mRNAs CODING FOR NEUROTOXIC PROTEINS

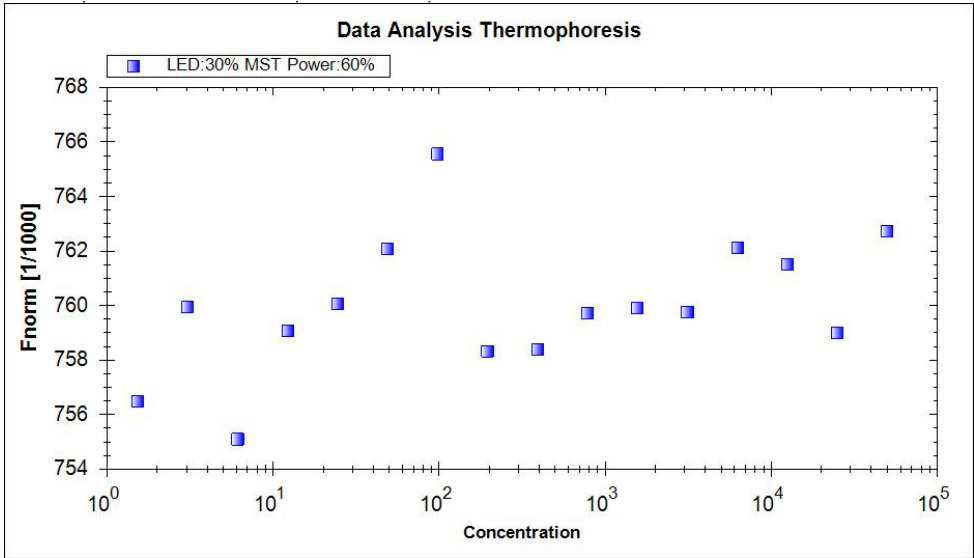


APP IRE/IRP1/Buntanetap
Kd 3.2 nM

Fitting for Kd Formular

Fitted Parameter	Fitted Value
Dissociation Constant	3.22+/-0.464
Fluo.Conc	2
Bound	758.35
Unbound	749.76
Amplitude	8.59

Buntanetap binds
specifically to the APP IRE,
but not to the ferritin IRE



Ferritin IRE/IRP1/Buntanetap
No Kd



NEUROTOXIC PROTEINS IMPAIR AXONAL TRANSPORT AND **CAUSE A TOXIC CASCADE**

HIGH LEVELS OF NEUROTOXIC PROTEINS

IMPAIRED AXONAL TRANSPORT

SLOWER SYNAPTIC TRANSMISSION

INFLAMMATION

DEATH OF NERVE CELLS

LOSS OF COGNITIVE AND
MOTOR FUNCTION

BUNTANETAP LOWERS LEVELS OF NEUROTOXIC PROTEINS

IMPROVED AXONAL TRANSPORT

INCREASED SYNAPTIC TRANSMISSION

NO INFLAMMATION

HEALTHY NERVE CELLS

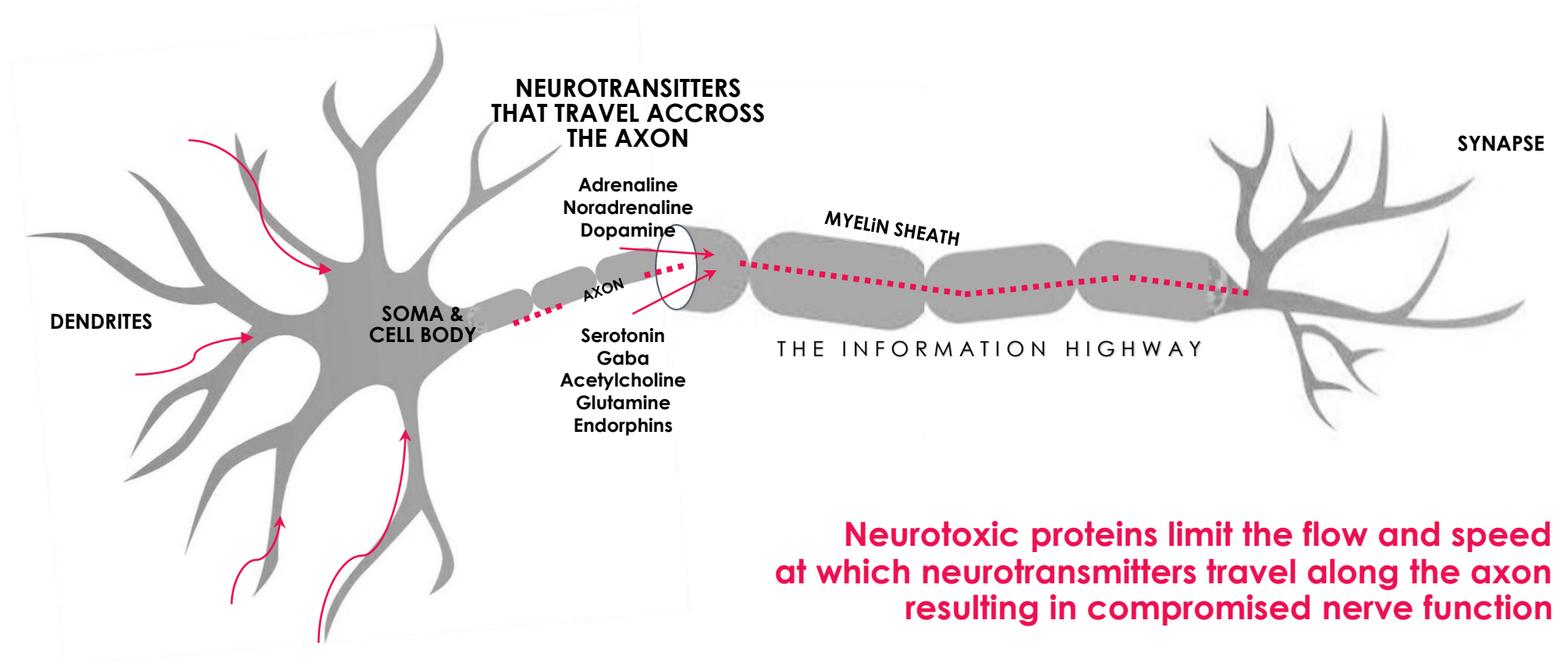
IMPROVED COGNITIVE AND
MOTOR FUNCTION

BUNTANETAP IMPROVES AXONAL TRANSPORT
AND **IMPEDES THE TOXIC CASCADE**



HOW NERVE CELLS WORK

In healthy nerve cells little packages containing neurotransmitters or nerve growth factors travel unimpaired from the cell body through the axon to the synapse.



NEURODEGENERATION IS AN AXONAL TRANSPORT DISEASE

“Axonal transport disruption is linked to human neurological conditions.”

- Nature Review, September 2019

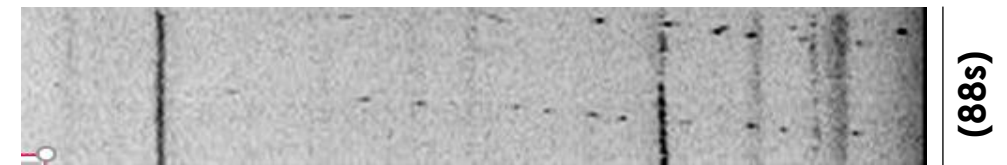
Axonal transport is responsible for:

- Neurotransmitters GABA (anxiety), ACh (cognition), dopamine (movement), serotonin (mood)
- Neurotrophic factors NGF, BDNF
- All communication within and between nerve cells

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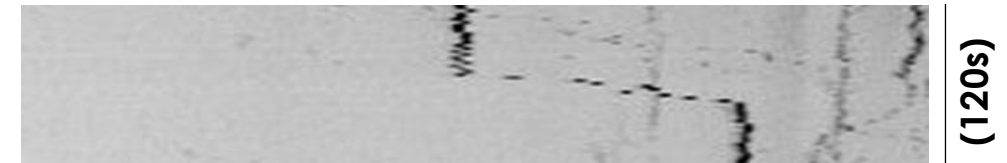
Normal Transport

The **Normal Flow and Speed** of vesicles carrying BDNF across the axon.



Abnormal Transport

Shows the **Blockage and Slowing** of BDNF across the axon. Black areas demonstrate where transport is slowed due to high levels of neurotoxic proteins.



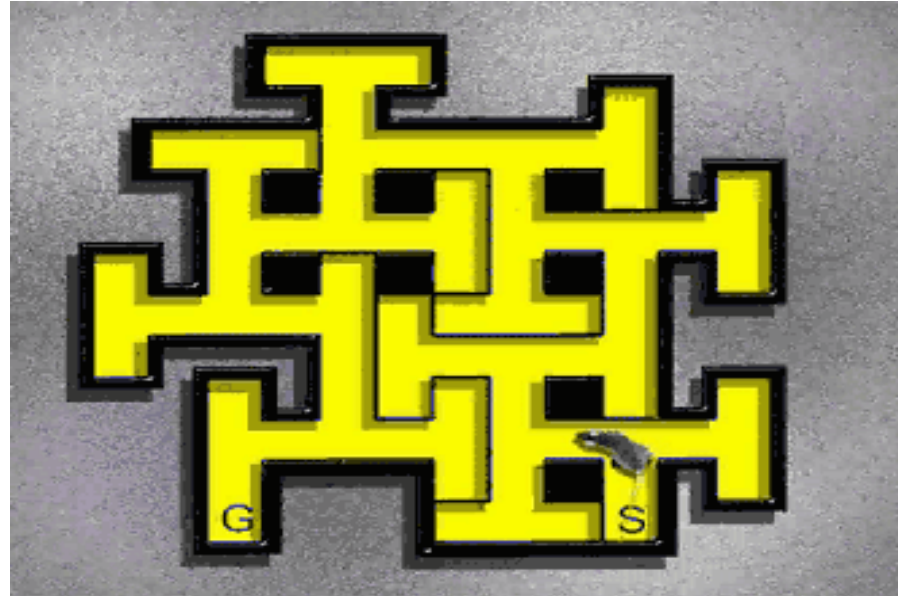
TREATED WITH BUNTANETAP

The **Flow and Speed** of axonal transport is improved.



RESULTS IN ANIMALS

Multiple animal studies showed that Buntanetap fully recovered the affected function



Function

Animal Model

Memory and learning (4)



AD mice, DS mice, stroke mice, TBI rats

Movement (2)



PD mice, FTD mice

Eyesight (1)



Acute glaucoma rats

TWO PHASE 2 CLINICAL TRIALS

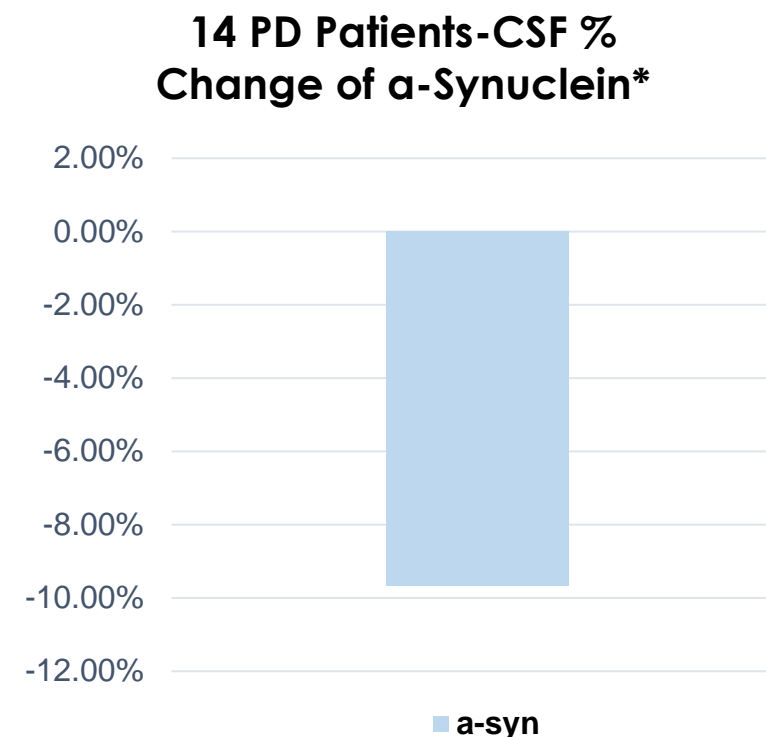
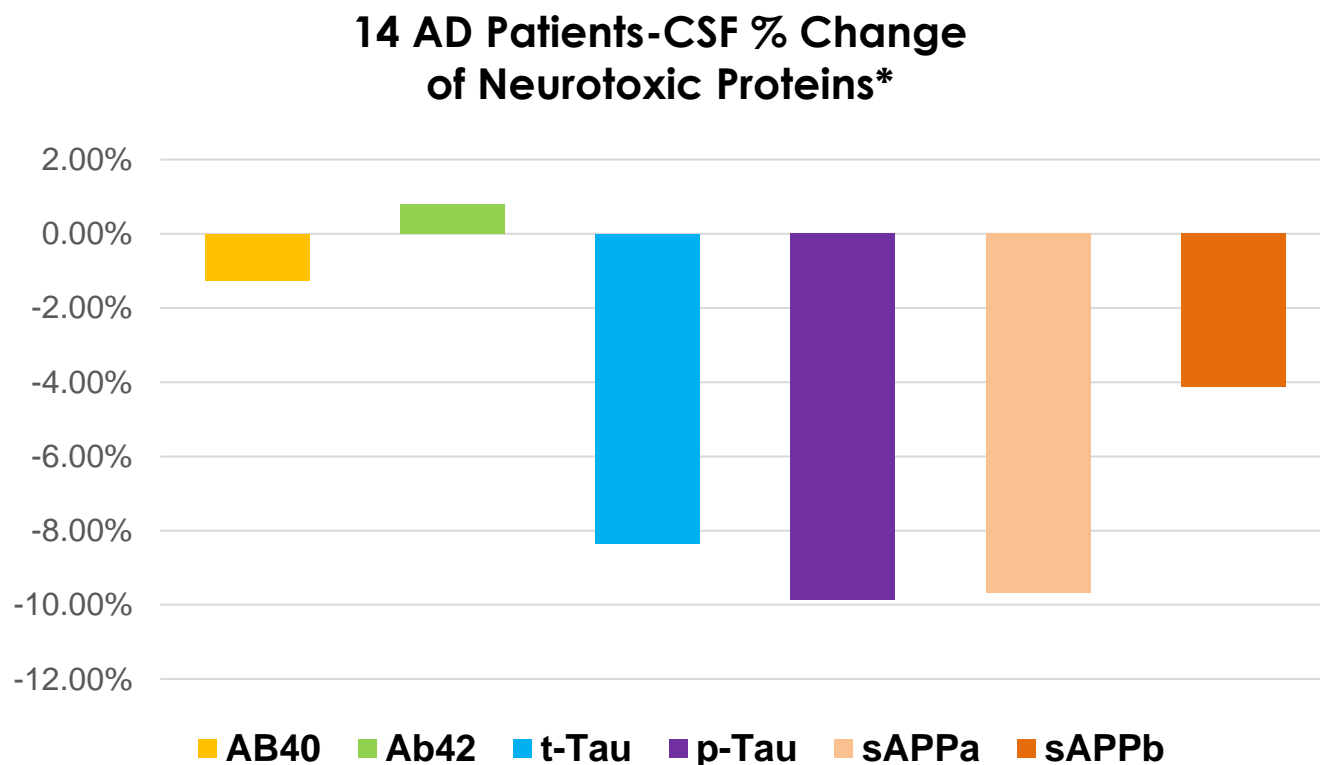
	AD Trial	PD Trial
Therapeutic Area	Early to Moderate AD and PD	
Phase	2	
Patients	14	14 + 40
Design	Double-Blind, Placebo-Controlled, Biomarker Study	
Dose	0 and 80 mg/day	0, 5, 10, 20, 40, 80 mg/day
Endpoints	Safety, PK	
Exploratory	Biomarkers, Efficacy	



BUNTANETAP MET THESE PRIMARY, SECONDARY & EXPLORATORY ENDPOINTS

- **Primary Endpoint** – SAFETY: Buntanetap is safe
- **Secondary Endpoint** – PHARMACOKINETICS: as expected from previous experiments
- **Exploratory Endpoints:**
 - BIOMARKERS: reduced as expected
 - COGNITION AND FUNCTION: improved ADAS-Cog and WAIS in AD patients and UPDRS and WAIS in PD patients

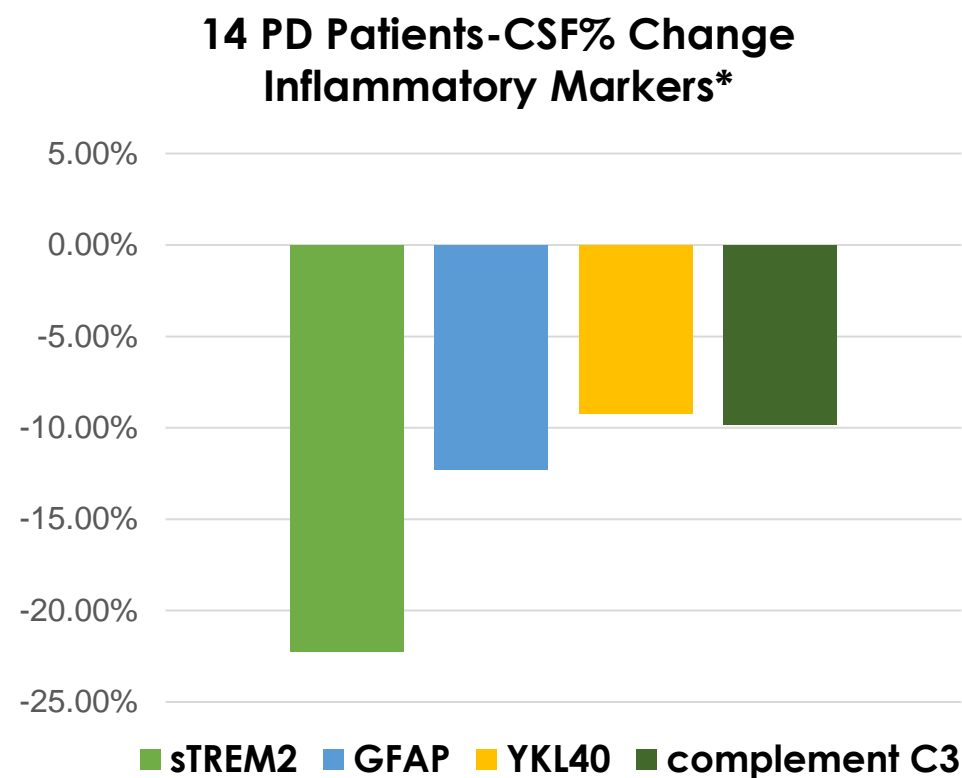
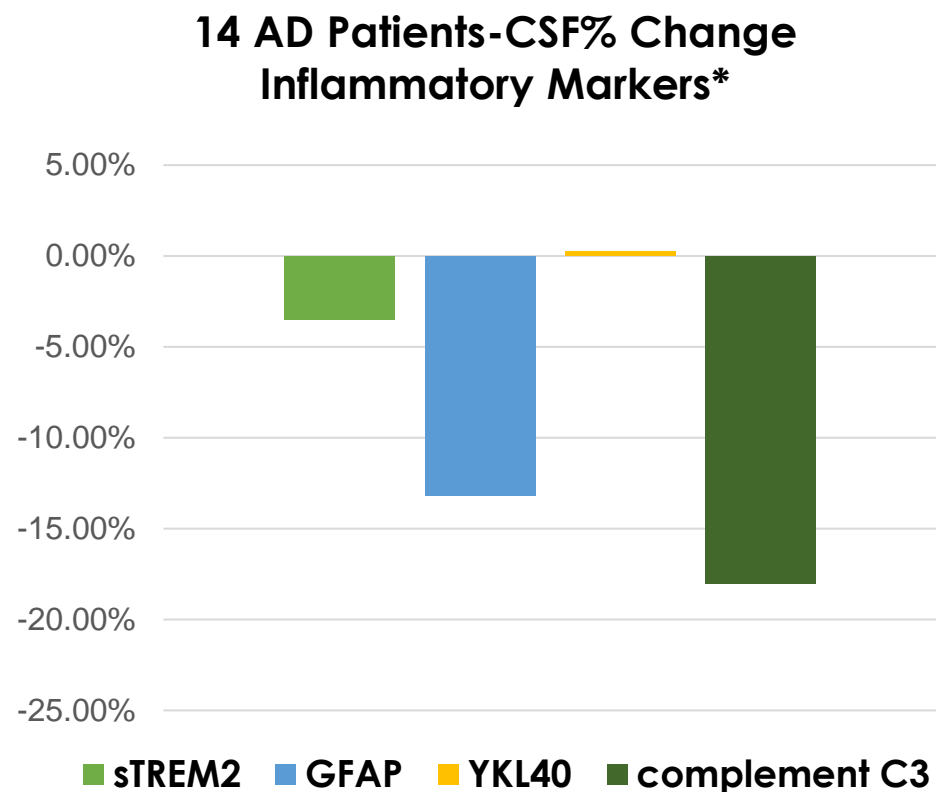
REDUCED NEUROTOXIC PROTEINS IN BOTH AD AND PD PATIENTS



APP (and its downstream products), and p-Tau are the neurotoxic proteins involved in AD, while a-Synuclein is the neurotoxic culprit of PD. The reduction compares well to the reduction seen in animals at full efficacy.

*All values are in comparison to placebo based on all data points

REDUCED INFLAMMATION IN BOTH AD AND PD PATIENTS

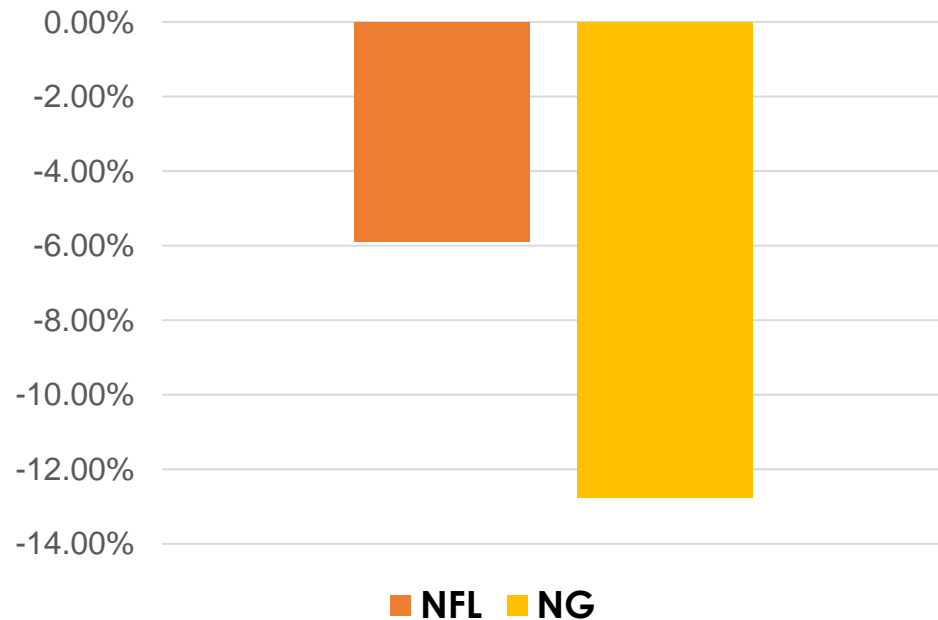


Inflammatory markers are lowered in AD and in PD patients, showing a normalization of inflammation in both neurodegenerative disorders.

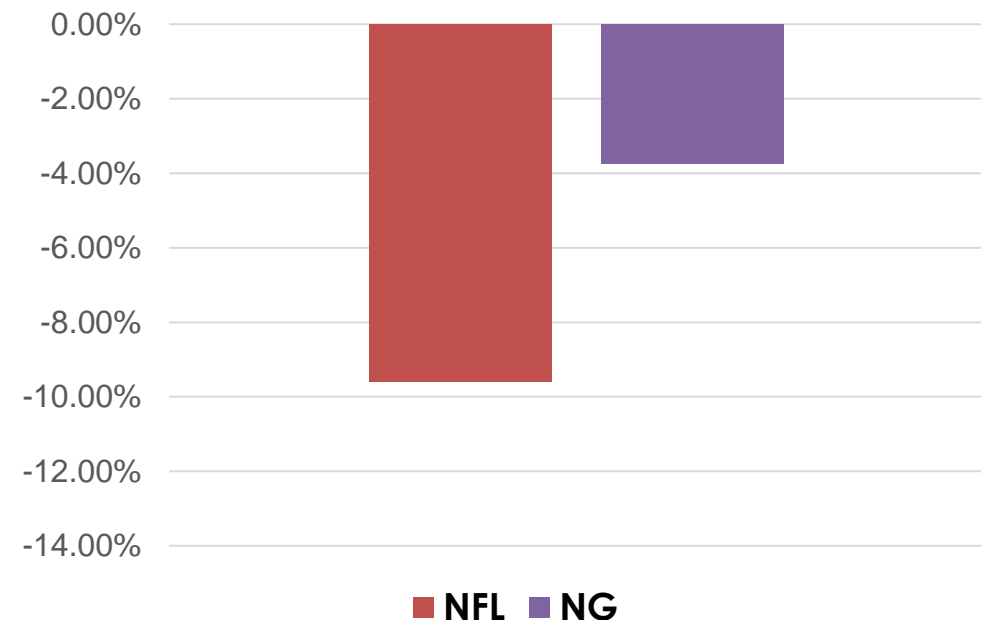
*All values are in comparison to placebo based on all data points

REDUCED AXONAL AND SYNAPTIC DYSFUNCTIONS IN BOTH AD AND PD PATIENTS

14 AD Patients-CSF % Change Axonal and Synaptic Markers*



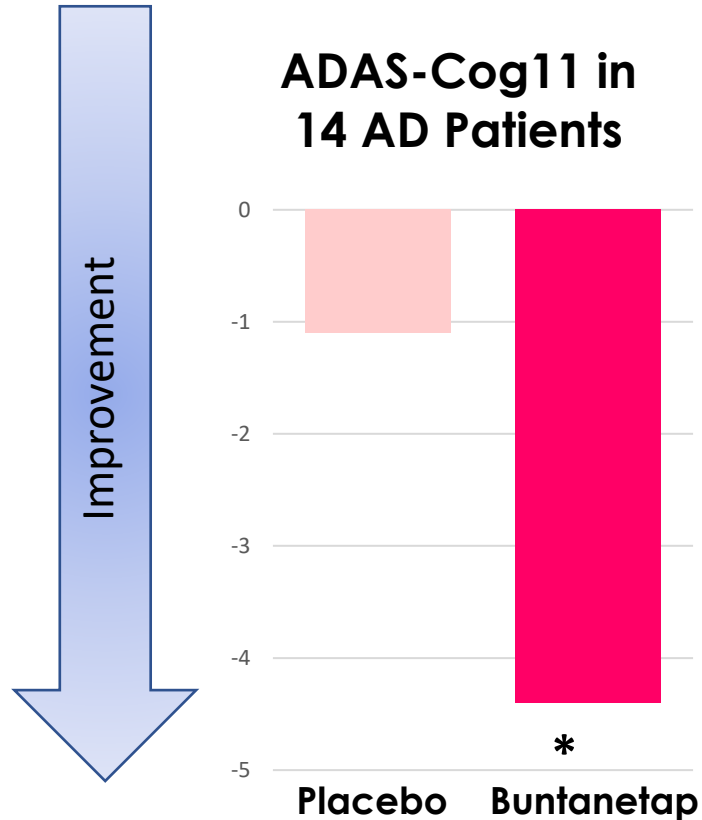
14 PD Patients-CSF % Change Axonal and Synaptic Markers*



Neuronal and synaptic markers are lowered in AD and in PD patients, showing that the nerve cells are healthier.

*All values are in comparison to placebo based on all data points.

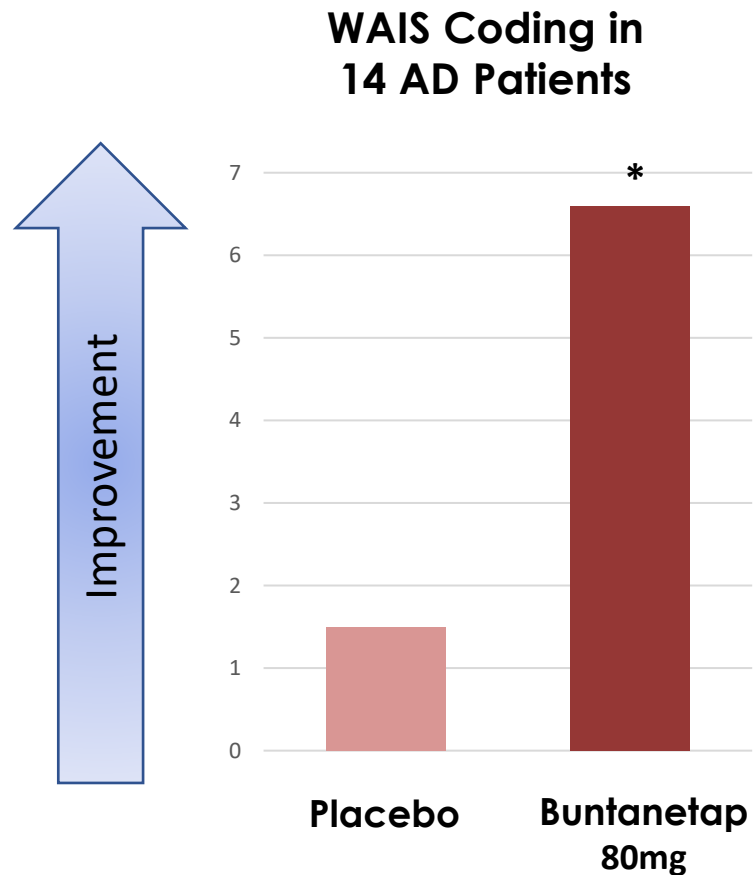
IMPROVED COGNITION IN AD PATIENTS - ADAS-Cog11



From baseline to 25 days in the Buntanetap-treated group, ADAS-Cog11 improved by 4.4 points, a statistically significant improvement of 30%. At 25 days the treated group is 3.3 points better than the placebo, an improvement of 22%.

In this presentation, statistical significance from baseline is shown by an asterisk on the top or bottom of the dose bar. Statistical significance from placebo is shown by an asterisk on a line from the placebo to the dose bar. * $p < 0.05$

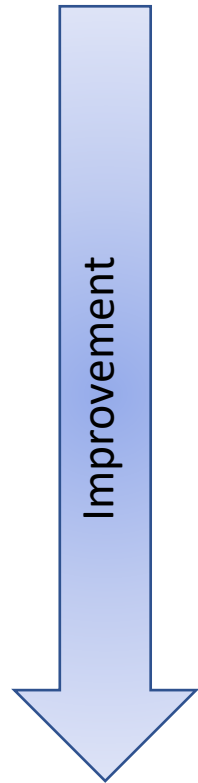
IMPROVED CODING SPEED IN AD PATIENTS - WAIS



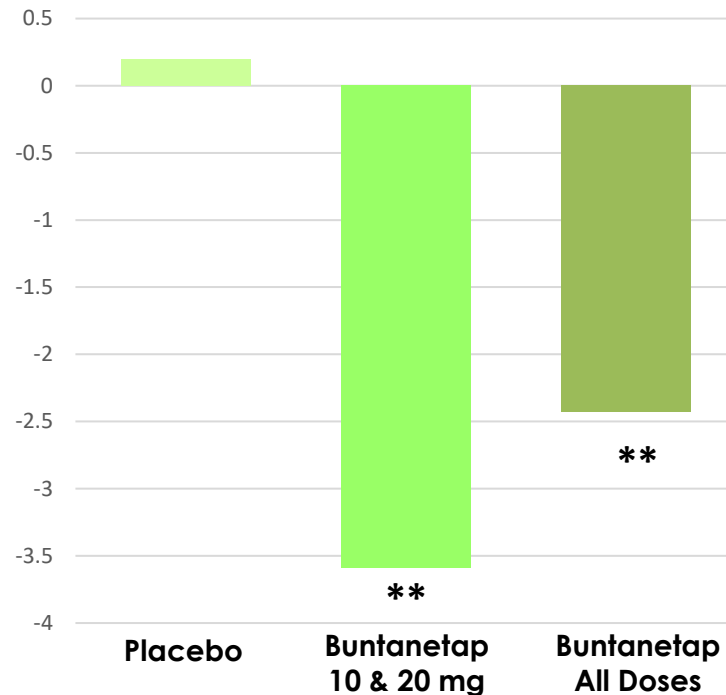
The WAIS coding test measures speed in movement and thinking. Treated AD patients show a 6.6 point statistically significant 23% improvement from baseline and a 4.9 point, 16% improvement from placebo.

* $P < 0.05$

IMPROVED MOTOR FUNCTION IN PD PATIENTS – MDS-UPDRS



**MDS-UPDRS Part III
In 54 PD Patients**

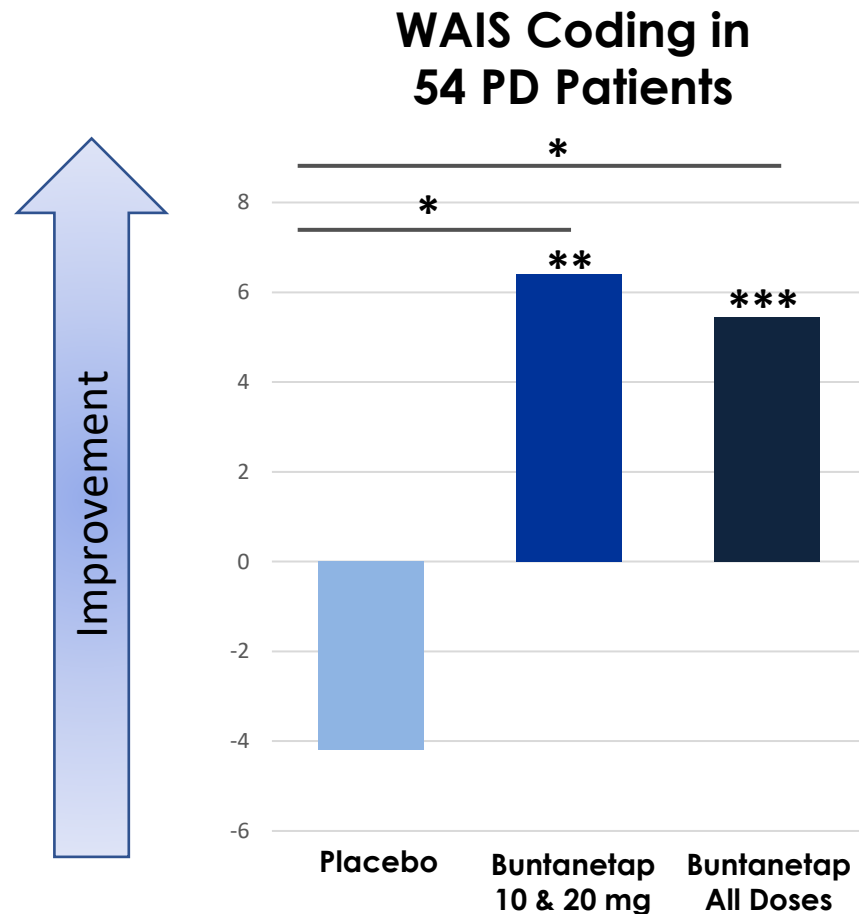


All doses of Buntanetap improved the MDS-UPDRS Part III individually. Combined as shown they improved the Part III score by 2.43 points (13.4%) compared to baseline (**p<0.01).

10mg and 20mg are the most efficacious doses and they improved the Part III score by 3.59 points (16.5%) in 25 days compared to baseline (**p<0.01).

Part II, IV and Total Scores are also improved.

IMPROVED CODING SPEED IN PD PATIENTS - WAIS



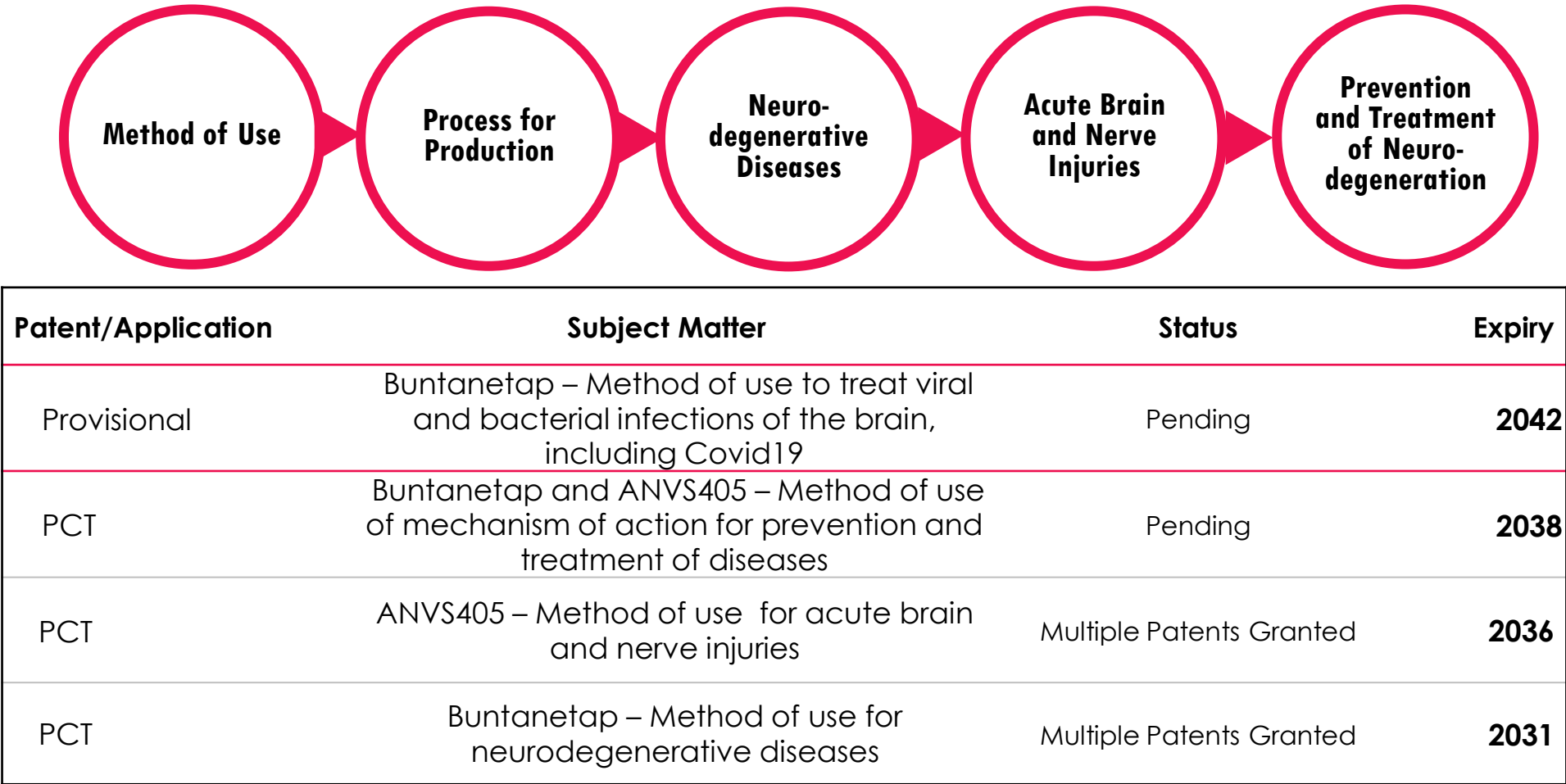
The WAIS coding test measures speed in movement and thinking. PD patients show a statistically significant improvement both from baseline (17.1% for 10+20mg; 13.5% for all doses combined) and from placebo (27.1% for 10+20mg; 23.4% for all doses combined).

* $p < 0.05$ ** $P < 0.01$

*** $P < 0.001$

CORPORATE PATENT ESTATE

Multi-layer strategy



PIPELINE

Therapy	Diseases/Conditions	PRE-CLINICAL	IND	PHASE I	PHASE II	PHASE III
Buntanetap Oral drug for chronic indications	AD					
	PD					
	AD-DS					
	FTD					
	CTE					
ANVS405 Injectable drug for acute traumatic events	TBI					
	Stroke					
ANVS301 Oral drug for advanced AD and dementia	Advanced AD					

The logo for Annovis, featuring the word "ANNOVIS" in white capital letters, with a red swoosh underline that starts under the first 'A' and ends under the 'S'.

FINANCIAL HIGHLIGHTS

- Completed \$50M equity raise in May 2021
- Cash balance \$47.5 million, debt \$0 as of September 30, 2021
- Fully funded through anticipated two Phase 3 trials / two years
- NIH grants funding ADCS Phase 2a trial in AD and chronic toxicology study
- ~38% insider ownership
- Shares outstanding 8.1 million; float 5.6 million

MANAGEMENT AND ADVISORY TEAM



Maria L. Maccacchini, PhD, Founder, President & CEO

Dr. Maccacchini founded Annovis in May 2008 to develop better therapeutics for Alzheimer's, Parkinson's and other neurodegenerative diseases. She was partner and director of two angel groups, Robin Hood Ventures and MidAtlantic Angel Group. Additionally, Dr. Maccacchini was the founder and CEO of Symphony Pharmaceuticals/Annovis, a biotech company that sold in 2001 to Transgenomic. She served as general manager of Bachem Bioscience, the US subsidiary of Bachem AG, Switzerland and Head Molecular Biology Mallinckrodt. Dr. Maccacchini did one postdoc at Caltech and one at the Roche Institute of Immunology; her PhD in biochemistry is from the Biocenter of Basel with a two-year visiting fellowship at The Rockefeller University.



Jeffrey McGroarty, CPA, MBA, Chief Financial Officer

Mr. McGroarty is a financial executive with experience in investor relations, working with analysts, creditors and financial institutions, planning and analysis, capital allocation, SEC communications and reporting, accounting, acquisitions and turnarounds. He is experienced in effectively managing complex projects, building professional relations and developing staff. Mr. McGroarty was previously employed as CFO of Safeguard Scientifics, Interim Controller at Cephalon, Inc., Vice President-Financial Planning and Analysis of Exide Technologies, Inc., and Senior Manager at PWC. His MBA is from the Wharton School of Business.



Cheng Fang, PhD, Senior VP of Research & Development

Dr. Fang is an experienced neuroscientist with more than a decade of experience in neurodegenerative diseases, with broad scientific knowledge and hands-on experience. Prior to joining Annovis, she was a scientific solution consultant with Clarivate Analytics where she worked on cutting-edge scientific projects with top-50 pharma clients. Previously, Dr. Fang was business development manager for Coriell Institute for Medical Research and an assistant professor at Boston University, where she designed and supervised projects focused on prion diseases and AD as a research team leader.



Eve Damiano, MS, RAC, Senior VP of Regulatory Operations

Ms. Damiano has spent over 35 years in the biotechnology sector, focusing on the definition and execution of regulatory strategies and GxP compliance, encompassing early phase development through commercialization. Ms. Damiano has held various senior management positions throughout her career, with experience garnered at companies including Centocor, MedImmune, OraSure Technologies and Vicuron Pharmaceuticals. Ms. Damiano holds an accomplished track record in the definition and execution of regulatory strategies, including the development of innovative solutions and effective management of projects and resources to meet company objectives.



William Mobley, MD, PhD, Chief Scientific Advisor

Distinguished Professor, Department of Neurosciences Florence Riford Chair for Alzheimer Research and Associate Dean for Neurosciences Initiatives at UC San Diego. He is a member of the National Academy of Medicine. His research focuses on the neurobiology of neurotrophic factor actions/signaling and on the hypothesis that malfunction of these mechanisms contribute to neuronal dysfunction in developmental and age-related disorders of the neurosystem.

SCIENTIFIC ADVISORY BOARD



Sidney Strickland, PhD, Chairman

Vice President and Dean for Educational Affairs and Research Professor, Patricia and John Rosenwald Laboratory of Neurobiology and Genetics at Rockefeller University. Dr. Strickland's laboratory investigates how dysfunction of the circulatory system contributes to Alzheimer's and other neurodegenerative disorders. He will serve as the Chairman of Annovis Bio's SAB.



Gregory Petsko, PhD

Dr. Petsko is a member of the National Academy of Sciences, the National Academy of Medicine, the American Academy of Arts and Sciences and the American Philosophical Society. His research interests are directed towards understanding the biochemical bases of neurological diseases like Alzheimer's, Parkinson's, and ALS discovering treatments (especially by using structure-based drug design), that could therapeutically affect those biochemical targets, and seeing any resulting drug candidates tested in humans. He has also made key contributions to the field of protein crystallography.



Jeffrey Cummings, MD

Dr. Cummings completed Neurology residency and a Fellowship in Behavioral Neurology at Boston University, Massachusetts. US training was followed by a Research Fellowship in Neuropathology and Neuropsychiatry at the National Hospital for Nervous Diseases, London, England. Dr. Cummings was formerly Professor of Neurology and Psychiatry, Director of Alzheimer's Disease Research and Director of the Center for Neurotherapeutics at UCLA. He was Director of the Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland and Florida.



Rudolph E. Tanzi, PhD

Dr. Tanzi has published over 500 research papers and has received the highest awards in his field, including the Metropolitan Life Foundation Award, Potamkin Prize, Ronald Reagan Award, Silver Innovator Award, and many others. He was named to TIME magazine's list of TIME100 Most Influential People in the World (2015), and received the Smithsonian American Ingenuity Award, the top national award for invention and innovation. He co-authored the popular trade books "Decoding Darkness", New York Times bestseller, "Super Brain", and international bestseller "Super Genes".

The image shows a vertical waterfall on the left side of the slide. Overlaid on the waterfall is the word "ANNOVIS" in white, with a red swoosh graphic. The letters are arranged vertically, with "S" at the top and "V" at the bottom.

SUMMARY AND NEXT STEPS

- Annovis has a novel approach to stop AD and PD
- Buntanetap shows improvements in Phase 2a clinical trials:
 - Cognition in AD patients
 - Motor function in PD patients
 - WAIS coding in AD and PD patients
- This is the first double-blind, placebo-controlled study that shows improvements in AD patients as measured by ADAS-Cog and in PD patients as measured by UPDRS
- The successful completion of our Phase 2 clinical trials is providing validation of our approach in two diseases and allows us to begin planning for Phase 3 trials



Improves **THE FLOW** of Axonal Transport
in Alzheimer's Disease and
Neurodegeneration

Symbol: **ANVS** (NYSE)

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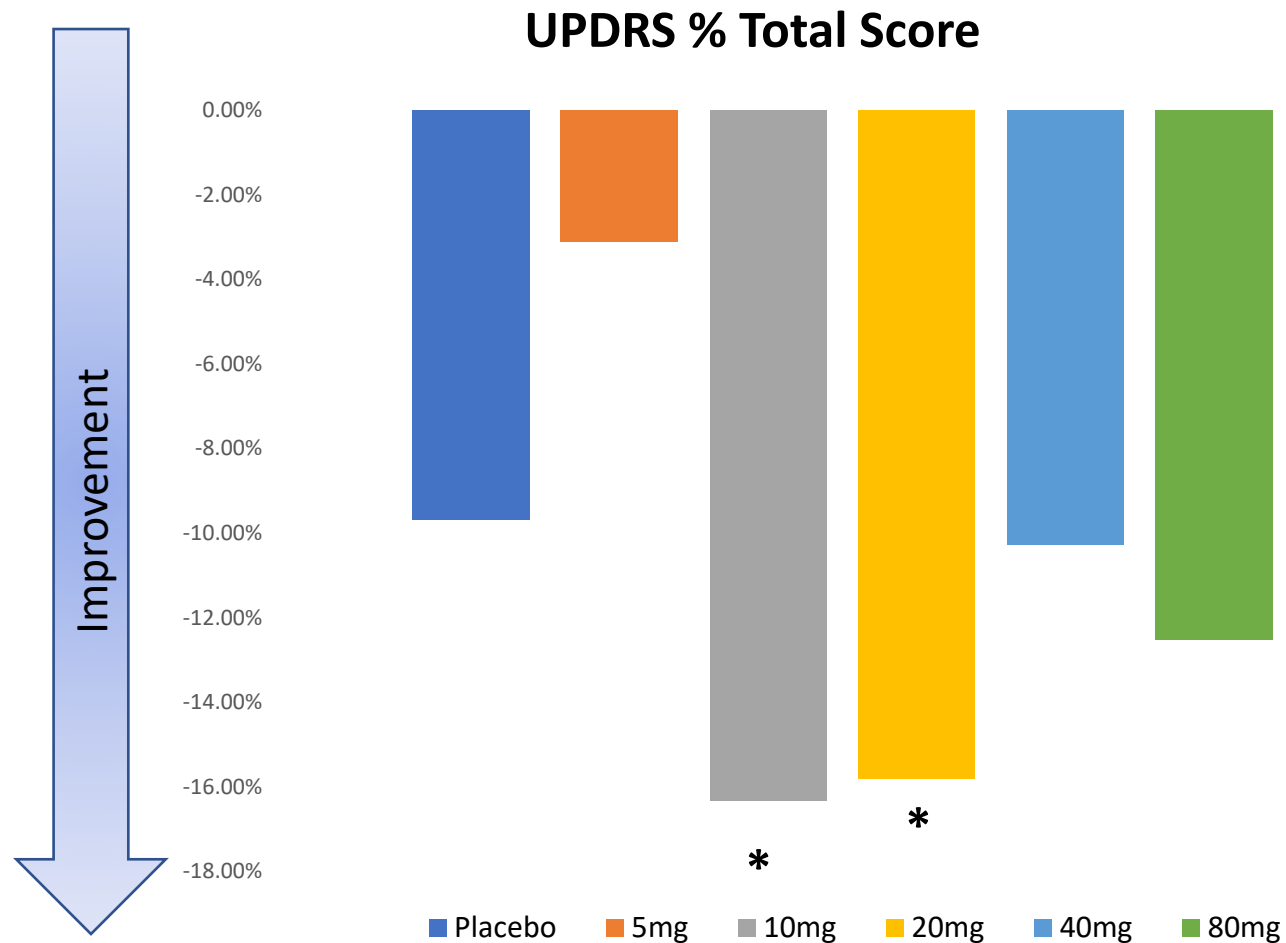
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IMPROVED FUNCTION IN PD PATIENTS

MDS-UPDRS Test

Data from 54 PD Patients



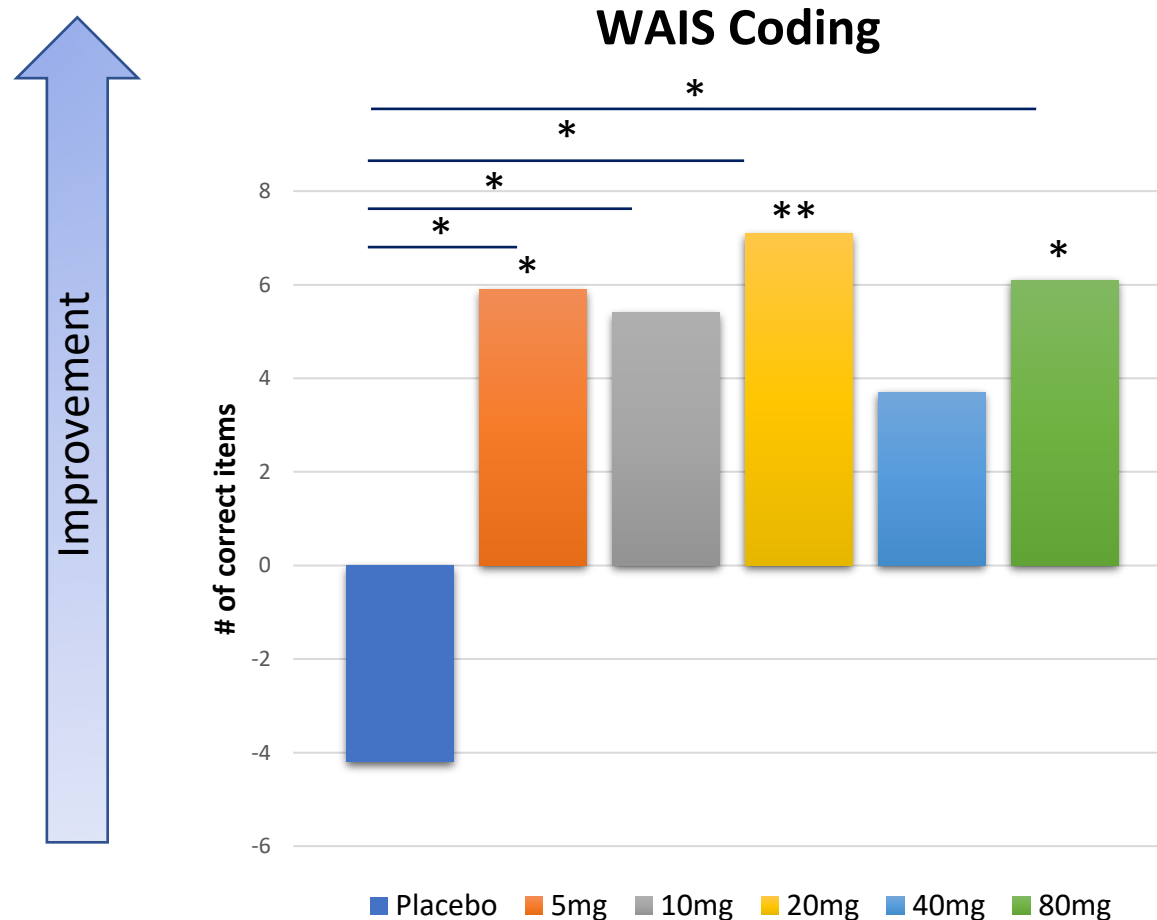
The MDS-UPDRS test showed the most improvements at 10 and 20 mg once per day

*p<0.05

IMPROVED SPEED AND ACCURACY IN PD PATIENTS

WAIS CODING TEST

Data from 54 PD Patients



Across the dose response the WAIS coding test showed improvements in speed of movement and coordination

* $p < 0.05$

** $p < 0.01$