Positive biomarker data corroborate the positive efficacy data in two phase 2 studies with ANVS401 in Alzheimer's and Parkinson's patients

Biomarkers for Alzheimer's Disease
August 26, 2021

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that clinical trials may be delayed; that the data reported herein is interim data, conclusions as to which may be superseded by subsequent data we expect to receive in connection with Phase 2a trials and/or subsequent clinical trials; and that any anticipated meeting with or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.

CHANGE IN CAUSES OF DEATH FROM 2000 TO 2018

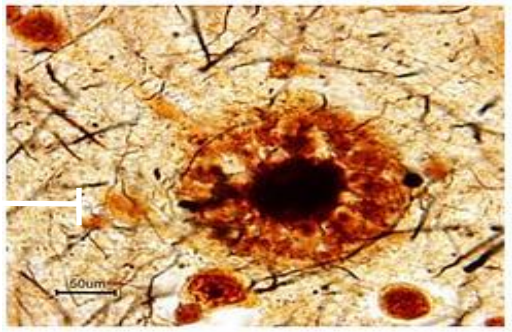
• Breast Cancer	- 13%
• Colon Cancer	- 21%
• Heart Disease	- 21%
• Stroke	- 24%
• HIV	- 67%
• Parkinson's	+ 84%
• Alzheimer's	+ 112%

ANNOVIS' NEW APPROACH TO ATTACK AD AND PD

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

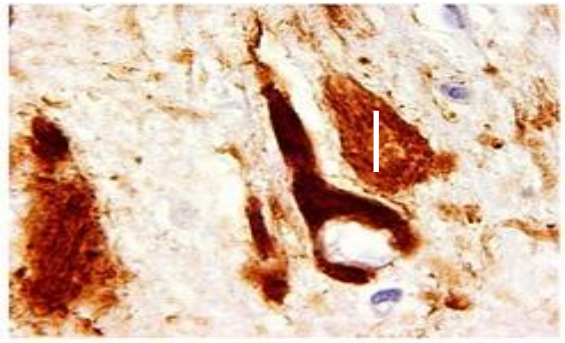
Amyloid β

Alzheimer's - Parkinson's
Aβ Targeting Compounds



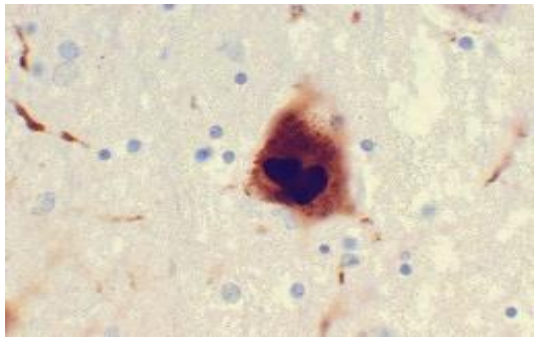
Tau

Tauopathies - Alzheimer's
Tau Targeting Compounds



aSynuclein

Parkinson's - Alzheimer's
aSYN Targeting Compounds



Attacking one neurotoxic protein results in minimal effect

ANVS401 is the only drug to attack multiple neurotoxic proteins simultaneously

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

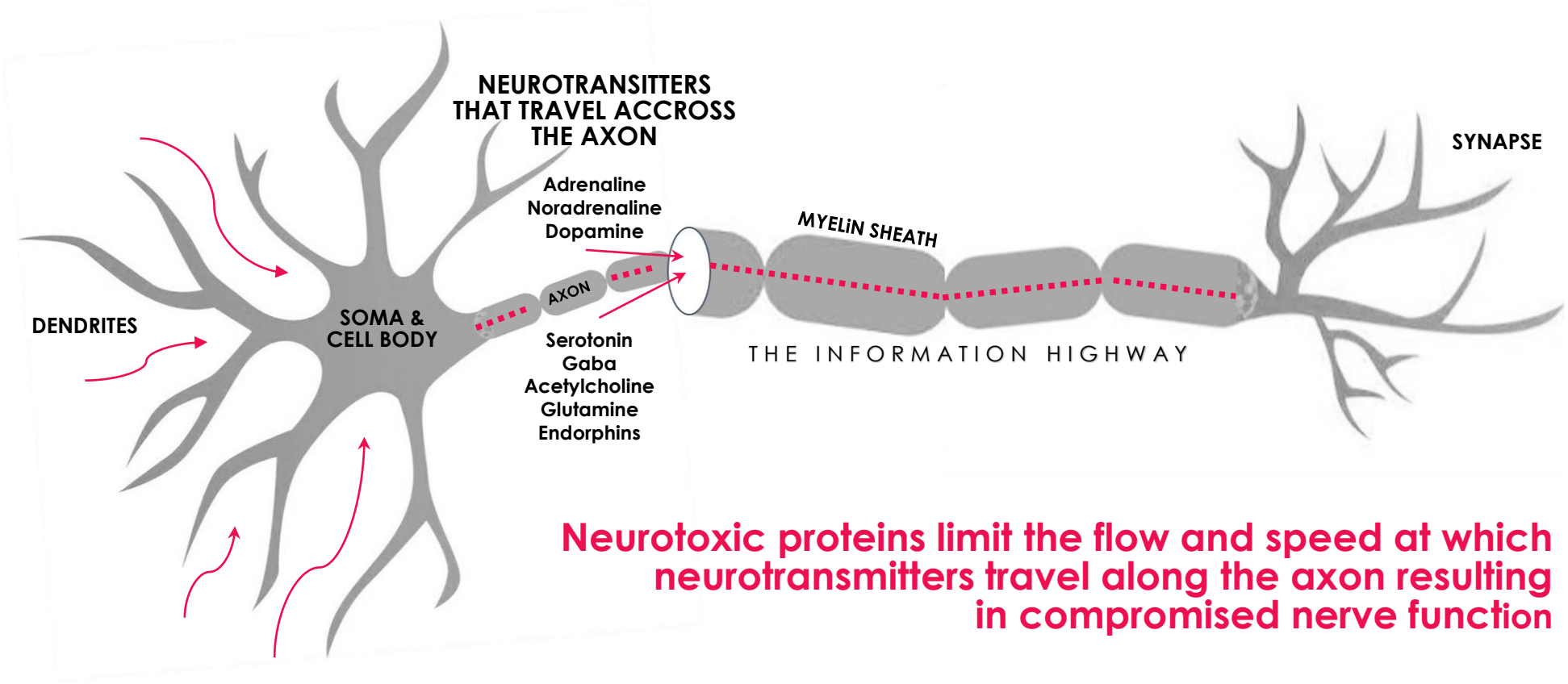
ANVS401 LOWERS LEVELS OF NEUROTOXIC PROTEINS

- IMPROVED AXONAL TRANSPORT
- INCREASED SYNAPTIC TRANSMISSION
- NO INFLAMMATION
- HEALTHY NERVE CELLS
- IMPROVED COGNITIVE AND MOTOR FUNCTION

ANVS401 IMPROVES AXONAL TRANSPORT AND **IMPEDES THE TOXIC CASCADE**

HOW NERVE CELLS WORK

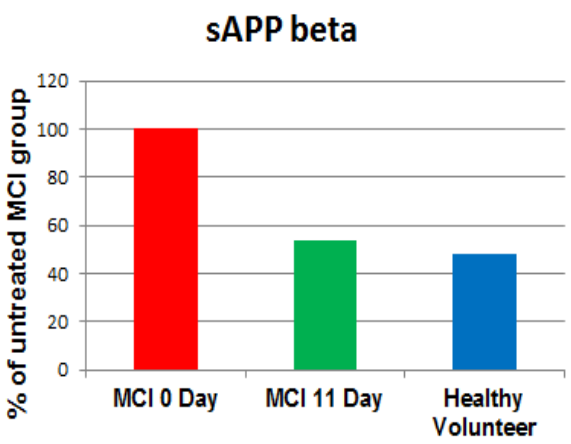
In healthy nerve cells little packages containing neurotransmitters or nerve growth factors travel unimpaired from the cell body through the axon to the synapse.

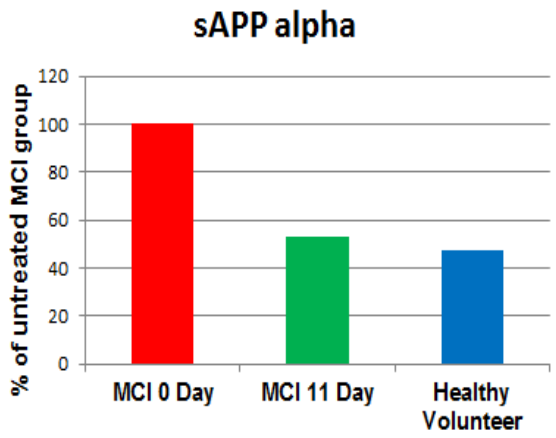


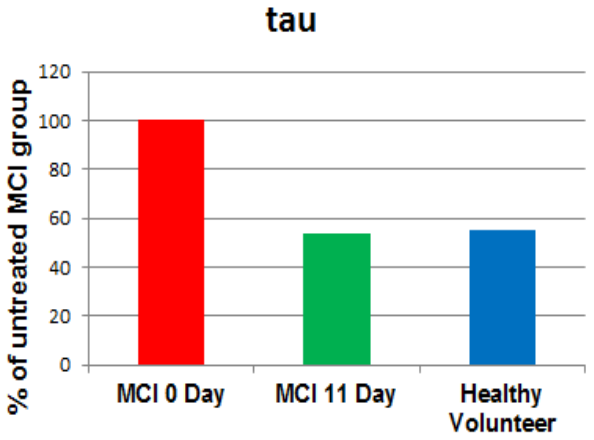
Neurotoxic proteins limit the flow and speed at which neurotransmitters travel along the axon resulting in compromised nerve function

STEP1 – LOWER NEUROTOXIC PROTEINS IN HUMANS

ANVS401 Lowers Neurotoxic Proteins in Spinal Fluid of MCI Patients







Maccecchini et al: JNNP 2012; 83: 894-902

- In this proof of concept study, ANVS401 lowers the levels of APP/Aβ, tau/p-tau and aSYN back to the levels seen in healthy volunteers
- It lowers the levels of the three neurotoxic proteins causing AD and PD

STEP 1 - ANVS401 LOWERS NEUROTOXIC PROTEINS

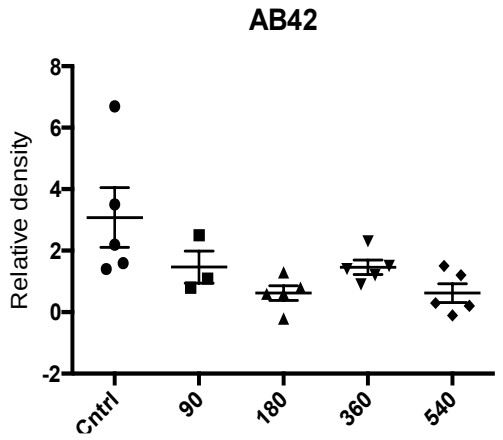
CSF Biomarkers Significantly Decrease After 10 Days of Oral ANVS401 in MCI Patients

Human Biomarker	CSF % of Baseline	p-Value
sAPP α	-59.9%	0.0006
sAPP β	-57.7%	0.0001
Aβ42	-51.4%	0.053
Tau	-46.2%	0.002
p-Tau	-61.0%	0.0005
αSYN	-41.2%	0.091

Maccecchini et al: JNNP 2012; 83: 894-902

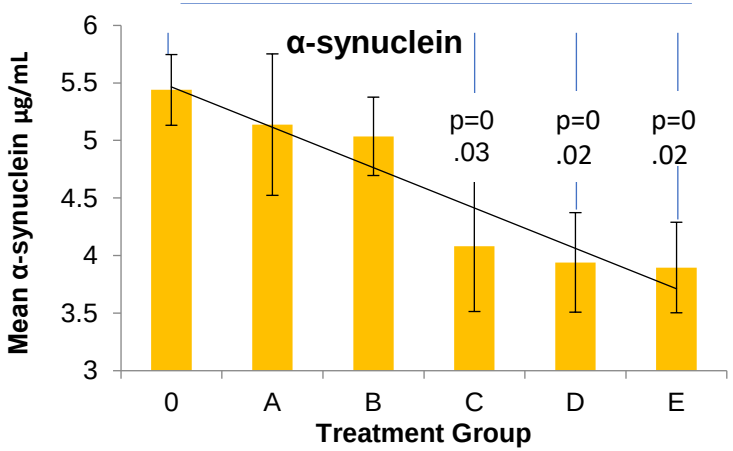
* Control Factor

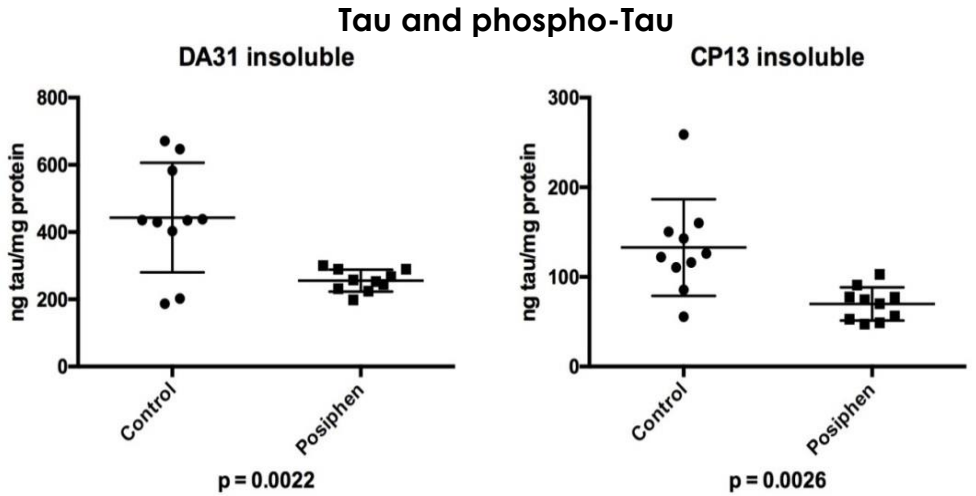
STEP 1 - LOWER NEUROTOXIC PROTEINS IN MOUSE BRAIN



Marker	(%) Drop	p-values
APP	39.8	0.008
CTFβ	46.8	0.0024
CTFα	48.5	0.0031
Aβ42	68	0.0008

ANVS401 lowers levels of the three neurotoxic proteins causing AD and PD APP/Abeta; Tau/p-Tau; alpha-synuclein





Teich et al: 2018; Kuo et al: 2019, Peter Davies et al

STEP 2 – ANVS401 RESTORES AXONAL TRANSPORT

"Axonal transport disruption is linked to human neurological conditions."

- Nature Review, September 2019

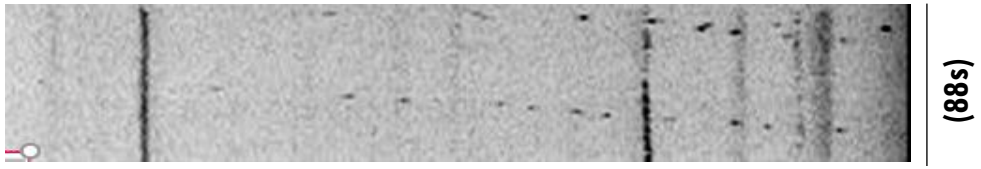
Axonal transport is responsible for:

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

Retrograde (0.5 frame/sec)

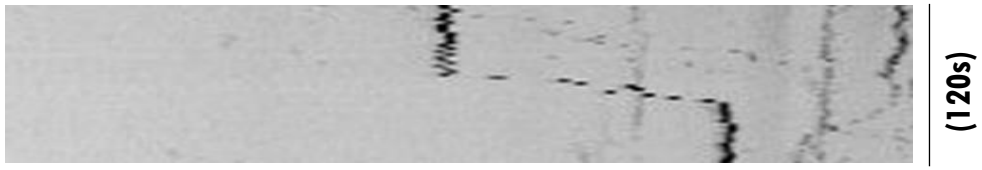
Normal Transport

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 ANVS401

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

APP, Ab42, C99 – Mobley, UCSD; aSYN – Isacson, Harvard; Lee, U.Penn;
Tau – U. Muenich & Zuerich; Htt – Mobley, UCSD; TDP43 – Taylor, Northwestern

STEP 3 - ANVS401 LOWERS INFLAMMATORY MARKERS

CSF Inflammatory Markers Significantly Decrease After 10 Days of Oral ANVS401 in MCI Patients

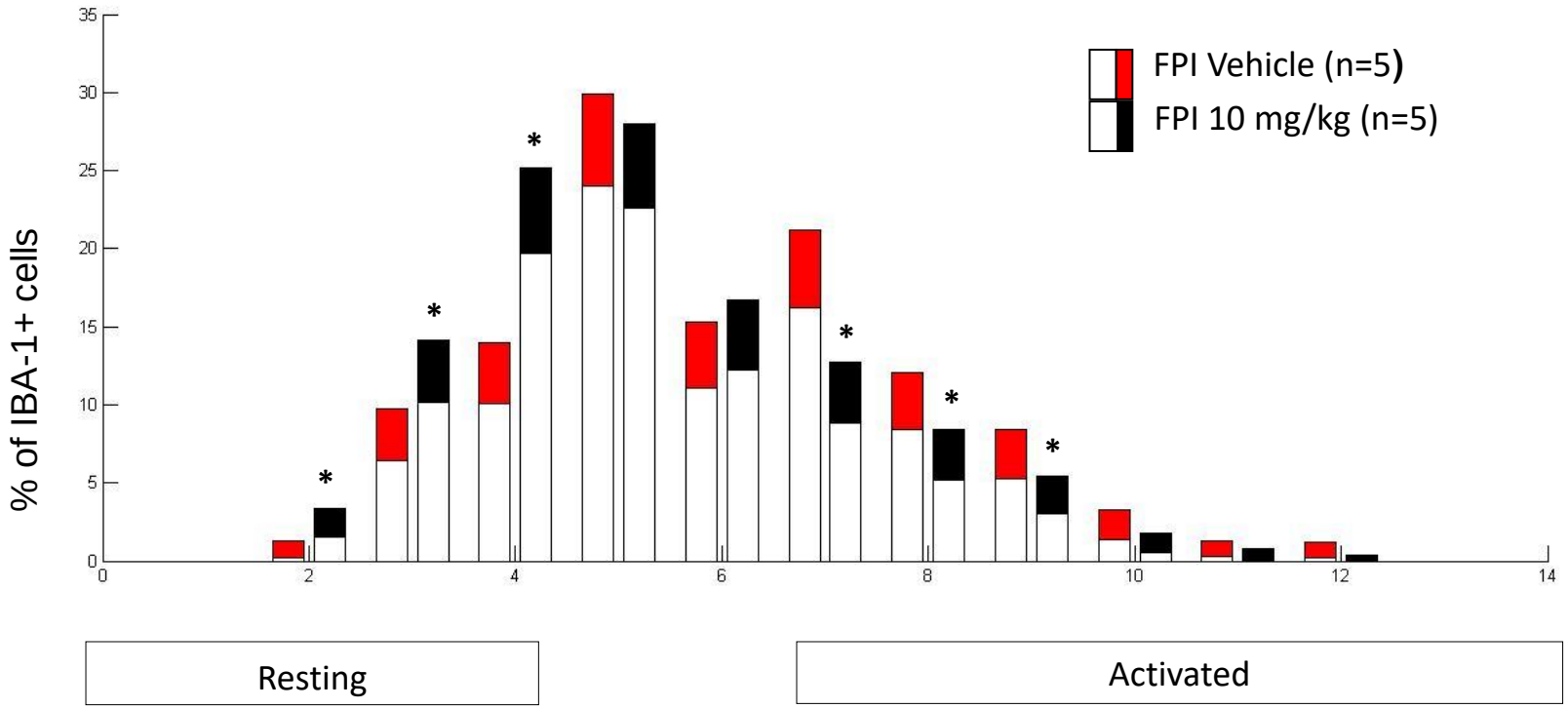
Inflammatory Protein	CSF % of Baseline	p-Value
Complement C3	-86.9%	0.0007
MCP-1	-87.5%	0.0007
YKL40	-72.7%	0.0113
sCD14	-26.1%	0.1159
Factor FH*	23.7%	0.4988

* Control Factor

Maccecchini et al: JNNP 2012; 83: 894-902

STEP 3 - INHIBITS MICRGLIA (INFLAMMATION) IN THE BRAIN

Data (Mean + 95% CI) analyzed with Bootstrapping method, *p<0.05



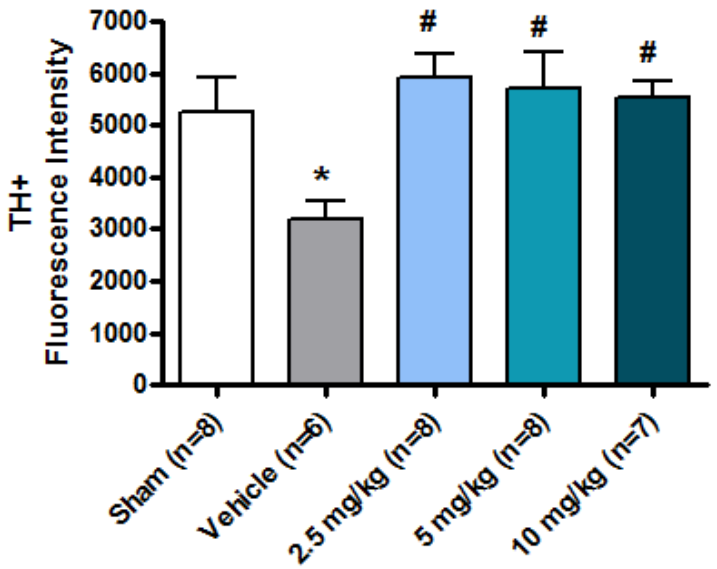
Microglial Cell Diameter (µm)

ANVS401 increases the number of resting microglia and reduces the number of activated microglia – it reduces inflammation

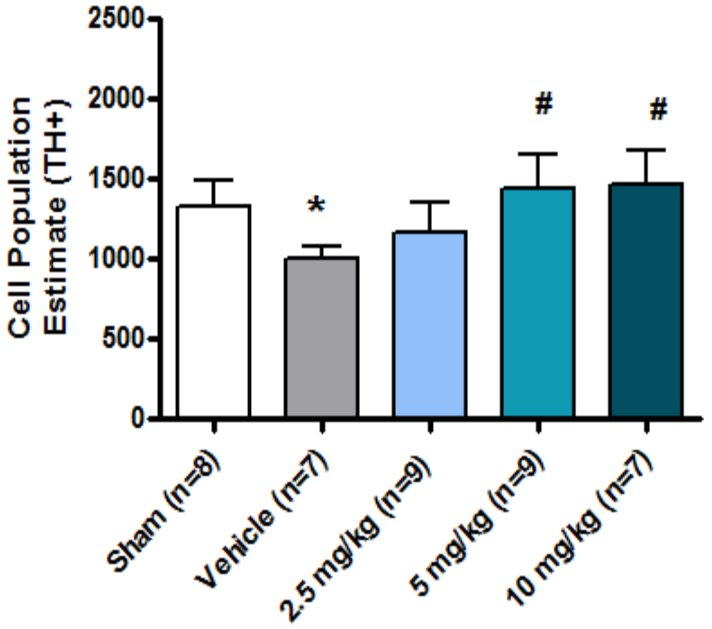
UCLA, Marie-Francoise Chesselet and David Hovda's lab

STEP 4 - PROTECTS NERVE CELLS FROM DYING

TBI injury on TH+ dopaminergic terminals in Striatum and reversal



TBI injury on TH+ dopaminergic neurons in S. nigra and reversal



Sham vs. vehicle groups, Student's t-test within lesion side, *p<0.05
Vehicle vs. treatment groups, One-way ANOVA of each lesion side, Bonferroni comparisons, #p<0.05

UCLA, Marie-Francoise Chesselet and David Hovda's lab, paper submitted for publication

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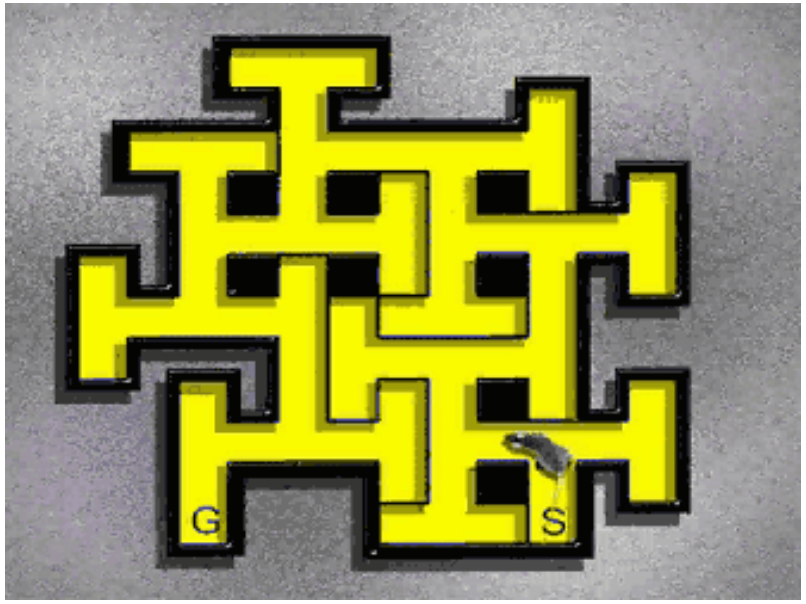
REVERSAL OF TOXIC CASCADE (STEP 1 T0 4) LEADS TO EFFICACY RESULTS IN ANIMALS

Multiple animal studies showed that ANVS401 fully recovers 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	Early to Moderate PD
Patients	14	14 + 40
Phase	2	
Sites	12	
Country	United States	
Design	Double-Blind, Placebo-Controlled, Biomarker Study	
Endpoints	Reversal of Toxic Cascade	
Exploratory	Efficacy	

BASELINE DEMOGRAPHICS

	ALZHEIMER			PARKINSON		
Patients Enrolled	Placebo (N=6)	ANVS401 80mg (N=10)	Total (N=16)	Placebo (N=5)	ANVS401 80mg (N=10)	Total (N=15)
Age (years)	68.0 (6.87)	72.8 (6.34)	71.0 (6.75)	75.4 (3.13)	65.0 (9.31)	68.5 (9.18)
Male	3 (50.0%)	2 (20.0%)	5 (31.3%)	3 (60.0%)	8 (80.0%)	11 (73.3%)
Female	3 (50.0%)	8 (80.0%)	11 (68.8%)	2 (40.0%)	2 (20.0%)	4 (26.7%)
HISPANIC	4 (66.7%)	5 (50.0%)	9 (56.3%)	2 (40.0%)	0 (0.0%)	2 (13.3%)
CAUCASIAN	2 (33.3%)	5 (50.0%)	7 (43.8%)	3 (60.0%)	10 (100.0%)	13 (86.7%)
WHITE	4 (66.7%)	8 (80.0%)	12 (75.0%)	5 (100.0%)	10 (100.0%)	15 (100.0%)
AFRICAN AMERICAN	1 (16.7%)	0 (0.0%)	1 (6.3%)	0	0	0
ASIAN	1 (16.7%)	1 (10.0%)	2 (12.5%)	0	0	0
NATIVE HAWAIIAN	0 (0.0%)	1 (10.0%)	1 (6.3%)	0	0	0

SAFETY SUMMARY

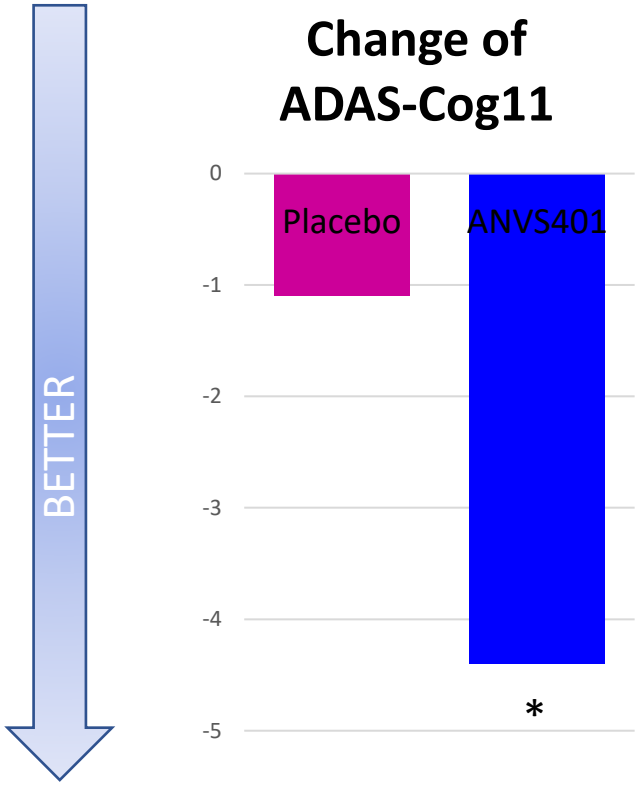
Data from first 14 AD and PD patients

	AD Patients			PD Patients		
	Placebo (N=6)	ANVS401 80mg (N=10)	Total (N=16)	Placebo (N=5)	ANVS401 80mg (N=10)	Total (N=15)
Subjects with any AEs	3 (50.0%)	5 (50.0%)	8 (50.0%)	3 (60.0%)	3 (30.0%)	6 (40.0%)
Number of AEs	4	7	11	5	3	8
Serious AEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AEs that led to Drug Interrupted	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AEs that led to Drug Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AEs Suspected Drug Related	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	0 (0.0%)	1 (6.7%)
AEs Study Procedure	3 (50.0%)	4 (40.0%)	7 (43.8%)	2 (40.0%)	1 (10.0%)	3 (20.0%)
CTCAE Grade 1	3 (50.0%)	4 (40.0%)	7 (43.8%)	3 (60.0%)	3 (30.0%)	6 (40.0%)
CTCAE Grade 2	0 (0.0%)	1 (10.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Most AEs were due to the spinal fluid collection that resulted in headaches and back aches

IMPROVED COGNITION IN AD PATIENTS – ADAS-Cog11

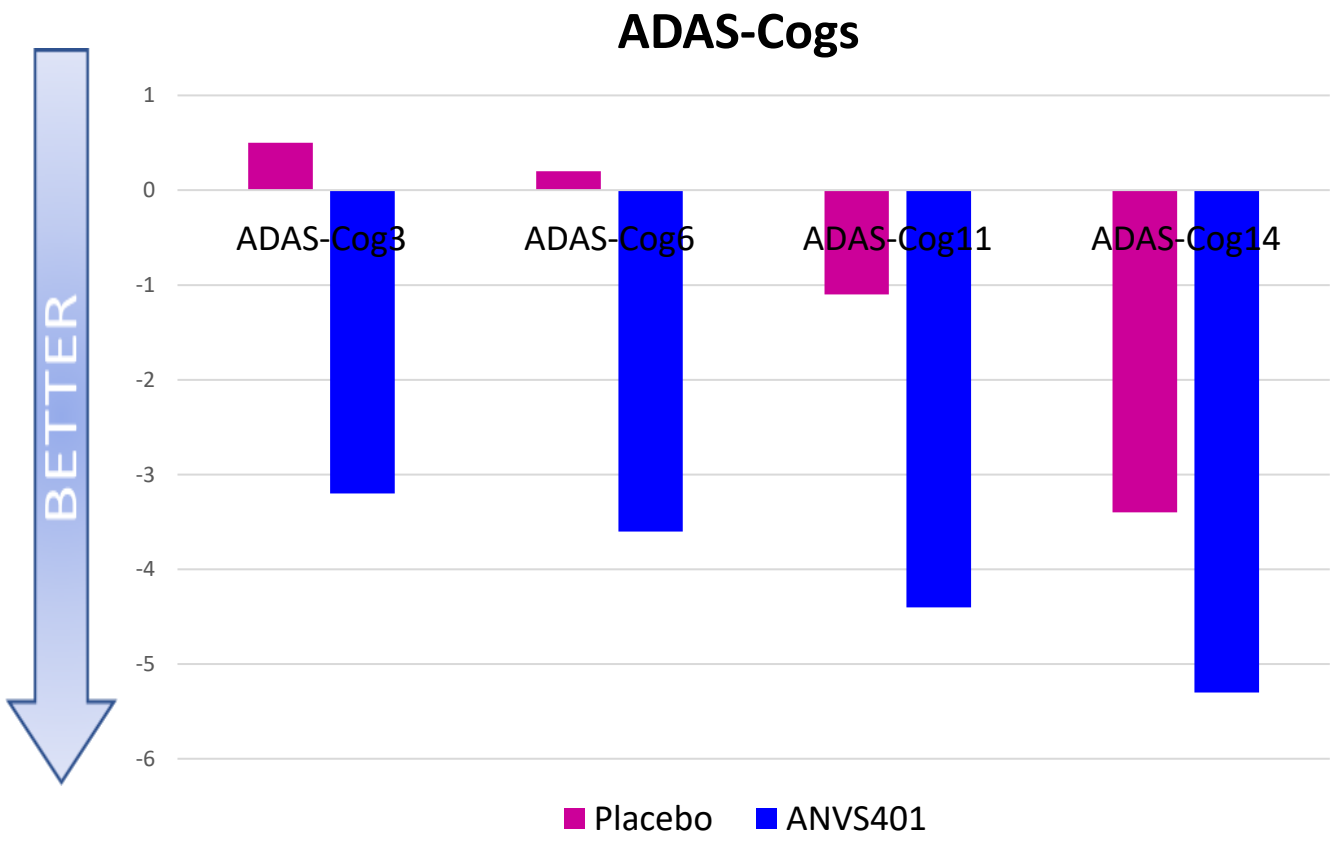
Data from 14 AD patients



From baseline to 25 days in the ANVS401-treated group, ADAS-Cog11 improved by 4.4 points, a statistically significant improvement of 30% ($p<0.05$). Compared to placebo at 25 days the treated group is 3.3 points better than the placebo

IMPROVED COGNITION IN AD PATIENTS – ADAS-Cogs

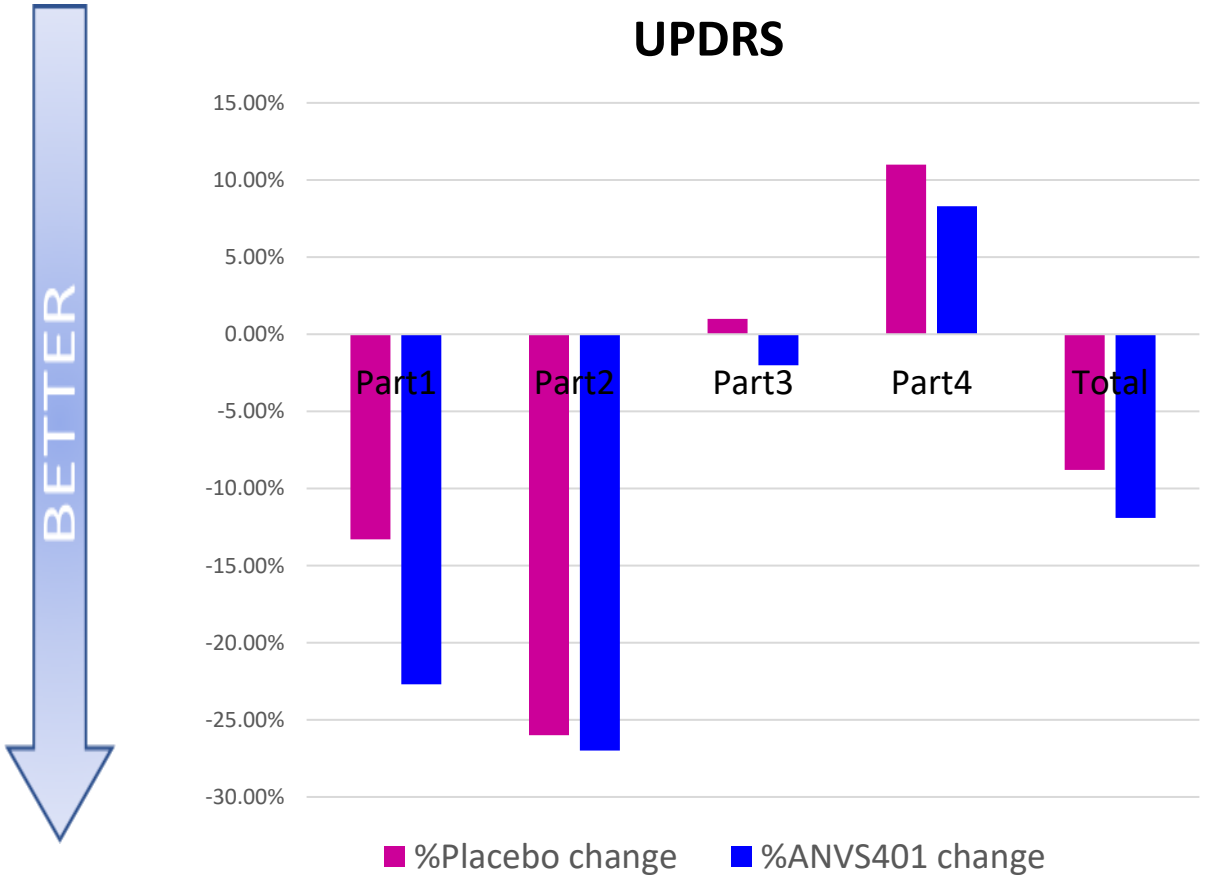
Data from 14 AD patients



While the whole ADAS-Cog 11 test is statistically significantly better in ANVS401-treated patients than in baseline, the ANVS401 group also shows trends of improvement in all four ADAS-Cog tests performed compared to placebo.

EFFICACY IN PD PATIENTS – MDS-UPDRS TEST

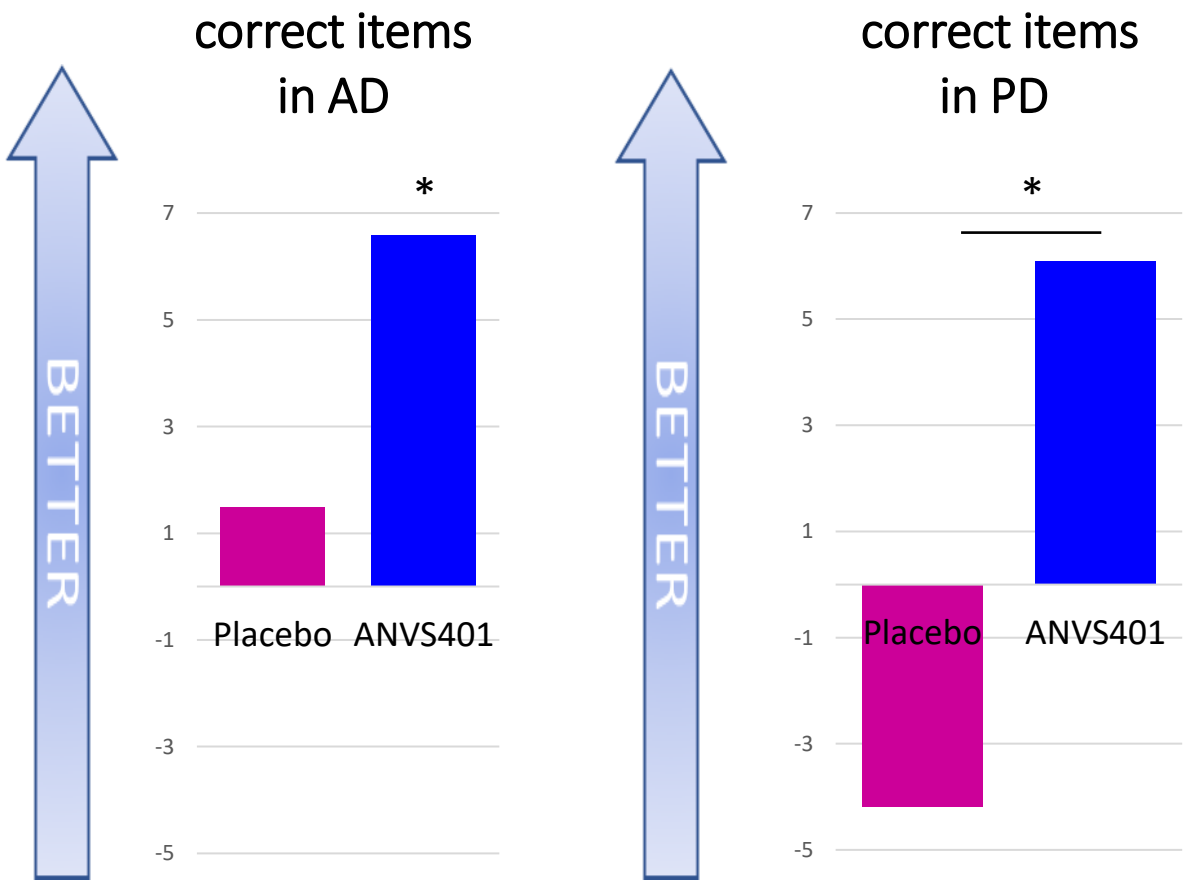
Data from 14 PD patients



ANVS401-treated group showed trends of improvement in all four parts of UPDRS test compared to placebo

IMPROVED SPEED AND ACCURACY IN AD AND PD PATIENTS
WAIS CODING TEST

Data from 14 AD and 14 PD patients



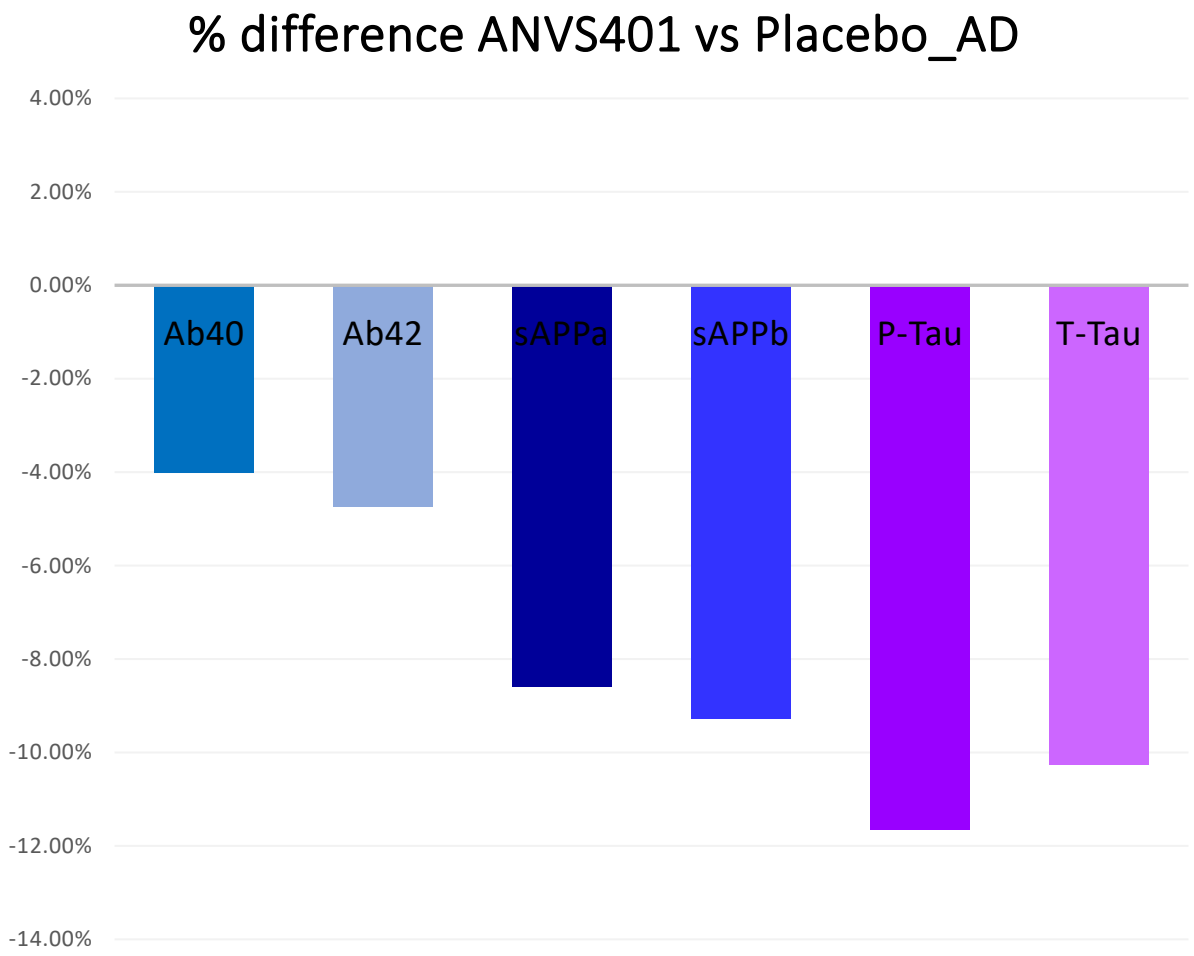
The WAIS coding test measures speed in movement and thinking. Treated AD patients show a statistically-significant 23% improvement and PD patients a statistically-significant 24% improvement compared with placebo

MARKERS OF TOXIC CASCADE

REVERSAL OF TOXIC CASCADE	
Step 1: Lower levels of neurotoxic proteins	sAPPa, sAPPb, Ab42, Ab40, Tau, P-Tau (alpha-Synuclein)
Step 2: Improved axonal transport	(BDNF)
Step 2: Improved axonal health	NFL
Step 3: Lower inflammation	sTREM2, YKL40 & GFAP
Step 4: Lower nerve cell death	(SNAP25, Neurogranin)

NEUROTOXIC PROTEINS ARE LOWERED IN AD PATIENTS

Data from first 14 AD



Aβ42/Aβ40 RATIO IN AD PATIENTS – IMPROVEMENT IN AD

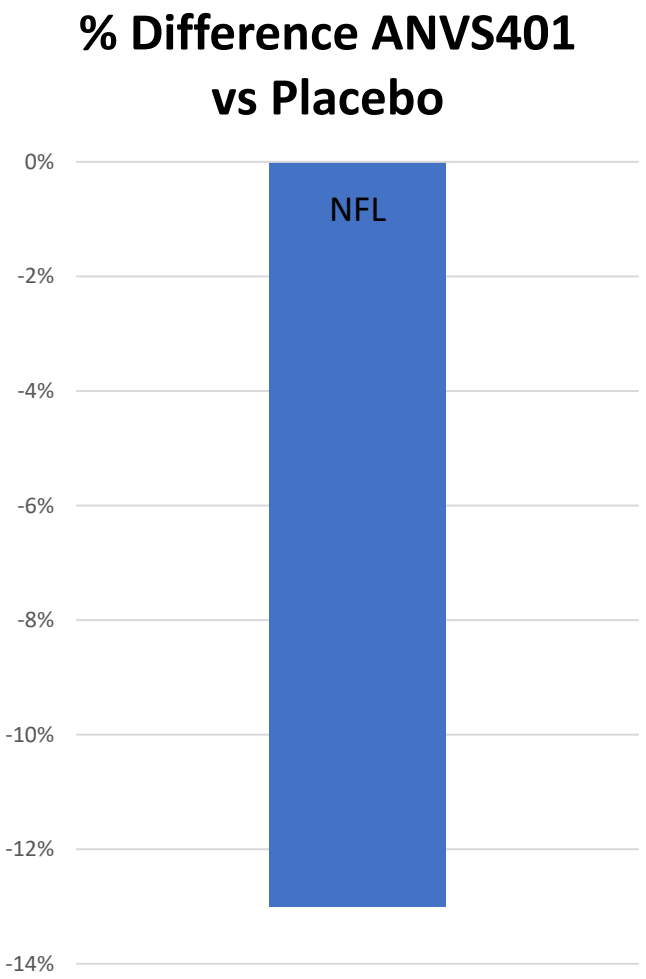
Data from first 14 AD patients

	AD Patients	
	Placebo	ANVS401
Baseline	0.064	0.059
25 Days	0.064	0.062
p-Value		0.0113

The Aβ42/Aβ40 ratio is well-accepted standard for AD. Patients with AD have a ratio **< 0.072** and patients without AD a ratio >0.072. ANVS401-treated patients improve their ratio statistically significantly after 25 days showing improvement in AD.

NEUROFILAMENT LIGHT IN AD PATIENTS IS LOWERED

Data from first 14 AD patients



Neurofilament light represents the health of the axon and neuron.

In ANVS401-treated patient populations, NfL is reduced representing better axonal health.

CONCLUSIONS

This study was designed to detect changes in biomarkers and the fact that some of the cognitive markers improve in a statistically significant way is noteworthy.

ANVS401 is the first drug that shows

- cognitive improvement by ADAS-Cog and WAIS in AD and
- functional improvement by MDS-UPDRS and WAIS in PD

in a double-blind placebo-controlled study


ANNOVIS
Thank You