# BioVie Day Presentation

March 23, 2023

# Forward-looking statements

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# Agenda

- Overview
- Chronic Low-grade Inflammation Science
- Development programs
  - Alzheimer's Disease
  - Parkinson's Disease
  - Epigenetics & Longevity
  - Liver Disease
- Clinical & Regulatory Strategy
- Commercialization Roadmap
- Social Impact
- Recap

# Overview

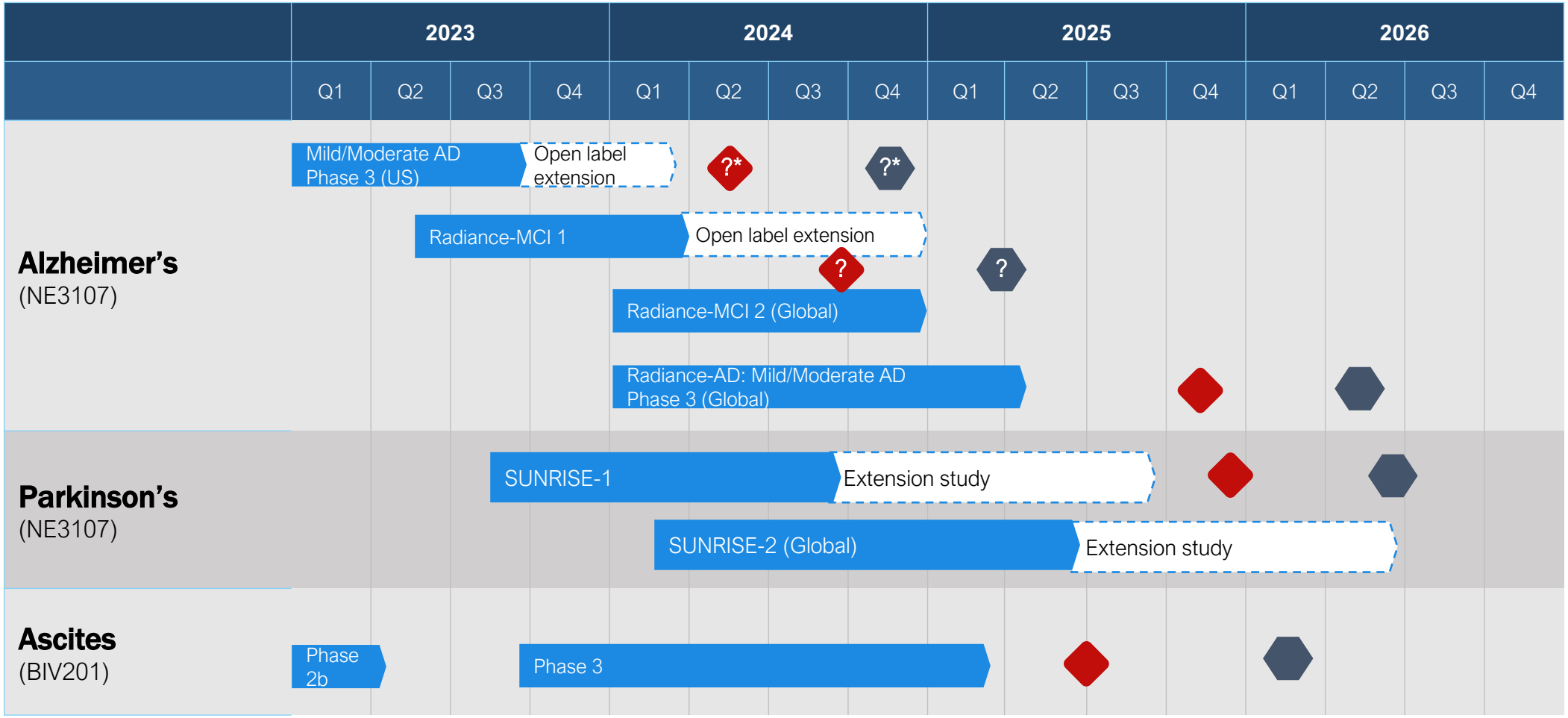
# Executive Summary

- The company is in the early stages of multiple late-stage data readouts for multiple indications addressing great unmet medical needs
- Early results in Alzheimer's Disease (AD), Parkinson's Disease (PD) and Ascites have all been encouraging, and our KOLs/SAB have encouraged us to move more assertively
- Potentially pivotal registrational trials are underway or will begin in 2023 for all indications
- Topline results from our Phase 3 AD trial expected to be announced October 2023. Regulatory submissions expected in 2024 and 2025
- We believe our portfolio, if approved, will create a platform of great benefit to patients and economic value to shareholders
- All development and commercialization options (including partnering) being considered
- Our support of Social Impact Partners allows us to bring better patient-centered support to affected individuals/families, of which our future medication will be an important part

# Our journey thus far

- BioVie started with a single program in refractory ascites with the backdrop that terlipressin (or any treatment) has never been approved in the US
- Acquisition of the Neurmedix assets (including NE3107) expanded our horizons
  - The team that discovered NE3107 sought to develop a new therapy for diabetes
  - Their understanding of systems biology and metabolic syndromes led to the insights on NE3107's unique MOA and value in areas beyond diabetes, including AD and PD
- We took a more assertive approach than big-pharma
  - Proceeded straight to a potentially pivotal Phase 3 in mild- to moderate-AD as our first trial in AD
  - Supported exploratory biomarker Phase 2 started afterwards that associated NE3107 with reversed cognitive decline and reduced p-Tau in MCI and mild-AD
  - Conducted larger PD DDI study than required to seek an efficacy signal in humans, which revealed impact on greater motor control and morning "on time"
- Strong data and counsel from KOLs/SAB leading us to be more expansive with our aspirations than originally plan

# Our journey ahead




* Two Phase 3 trials are usually required for registration. However, the FDA has allowed filing based on strong data from a single pivotal trial in indications with few therapeutic options.

# Chronic Low-grade Inflammation Science

# Chronic low-grade inflammation

- Inflammation is the result of the body's natural protective processes

| Insults | Responders | Master Alarms | Pro-inflammatory factors |
|---|---|---|---|
| • Pathogens | • Blood proteins | • NFκB transcription factors | • Cytokines |
| • Trauma | • Platelets | • Oxidative stress | • Chemokines |
| • Ischemia | • Granulocytes | • Reactive oxygen | • Receptors |
| • Stress | • Monocytes | • Reactive nitrogen | • Complement factors |
| • Radiation | • Macrophages | | • Metalloprotinases |
| • Obesity | • Microglia | | • Cell adhesion molecules |
| • Cancer | • Endothelial cells | | |

- If insults and pro-inflammatory factors eliminated, pathology addressed
- If not, low grade chronic inflammation and associated insulin resistance ensues
- Inflammation and insulin resistance go hand-in-hand

# TNFα-mediated inflammation leads to many downstream consequences

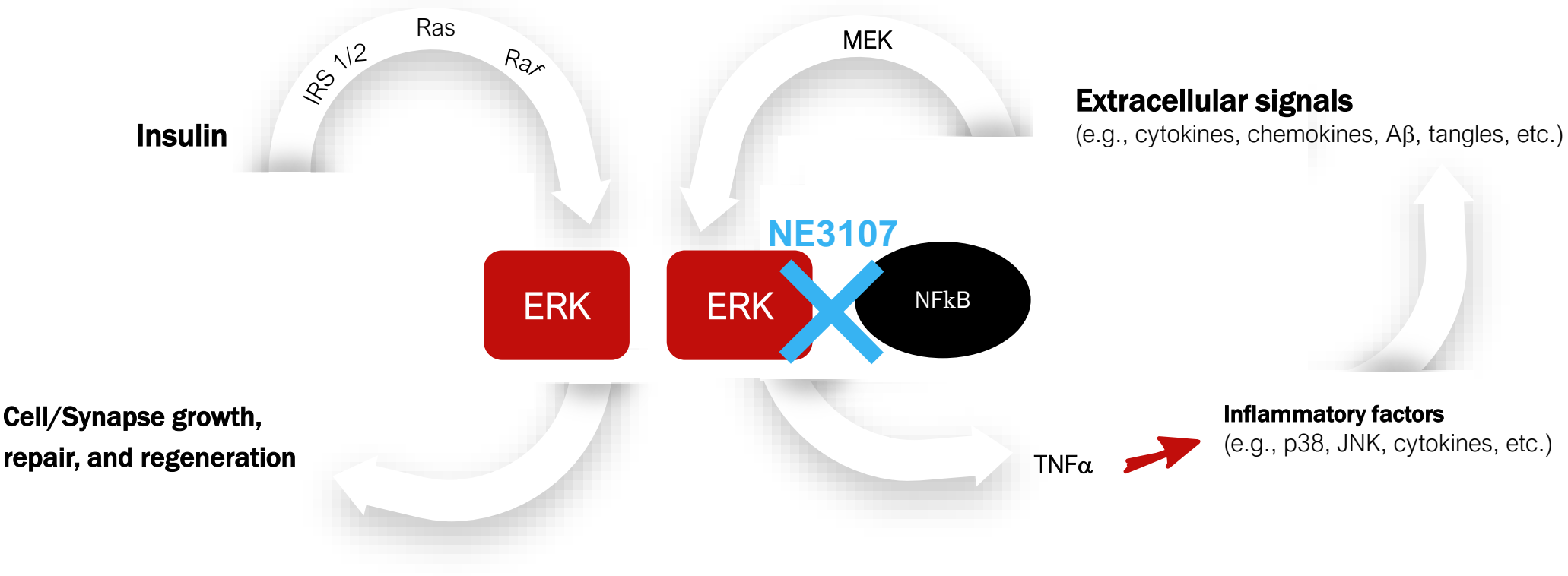
**TNFα**

- Cytokine and chemokine production (more inflammation)
- Systems dysregulation (diabetes, dyslipidemia, cardiovascular, etc.)
- Hypermethylation of DNA
- IKKβ and JNK activation → insulin resistance
- More APP → more Aβ (more inflammation)
- Serine/threonine kinase activation (Tau → pTau)

- Various forms of cancers
- Age-related cognitive impairment and dementia
- Parkinson's disease
- Cardiovascular disease
- COPD and respiratory disease
- Chronic kidney disease
- Inflammatory bowel disease
- Sepsis
- Many others

Wang Z *Nucleic Acids Research,* 2020, Vol. 48, No. 5; Sugden K *Neurology* 2022;99:e1402-e1413; Tang X DOI: 10.1002/mds.29157; Tabaeia S Artificial Cells, Nanomedicine, and Biotechnology, 47:1, 2031-2041; Qiu W *Am J Respir Crit Care Med* Vol 185, Iss. 4, pp 373–381, Feb 15, 2012; Rysz C *Int. J. Mol. Sci.* 2022, 23(13), 7108; Kraiczy J *Mucosal Immunology* volume 9, pages 647–658 (2016); Rump K *Sci Rep* 9, 18511 (2019)

# NE3107 blocks inflammatory (but not homeostatic) ERK and NFkB, which play pivotal roles in AD pathogensis



# Activation of Inflammatory Signaling

**Inflammatory signals (Amyloid beta, TNF, LPS, fatty acids, others) interact with toll-like receptor 4 (TLR4) and with TNF Receptor 1 (TNFR1) leading to:**

01 Activation of I kappa B kinase beta (IKKβ)

02 Phosphorylation of NFκB p105, which is degraded to p50

03 Release of MAP3K8 phosphorylation of MEK. ERK, RSK, MSK, NFκB3 (RelA p65)

04 Nuclear localization of p50 and phospho-p65

05 Transcription of kappa B (κB) **promoter** sites for inflammatory genes (e.g., TNF, IL-1, IL-6)

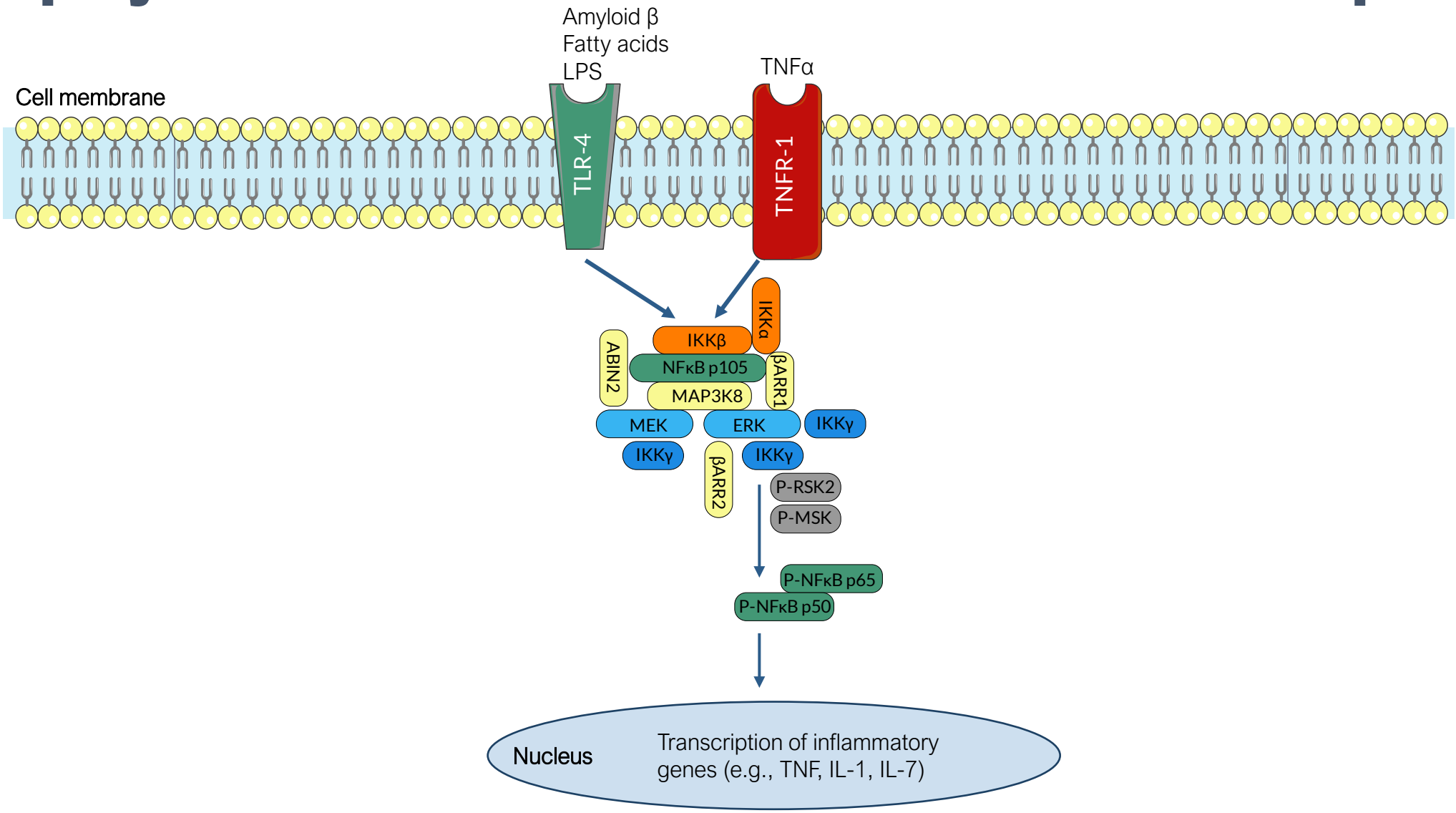
06 Translation, maturation and secretion of inflammatory mediators (e.g., TNF)

07 TNF binding to TNFR1

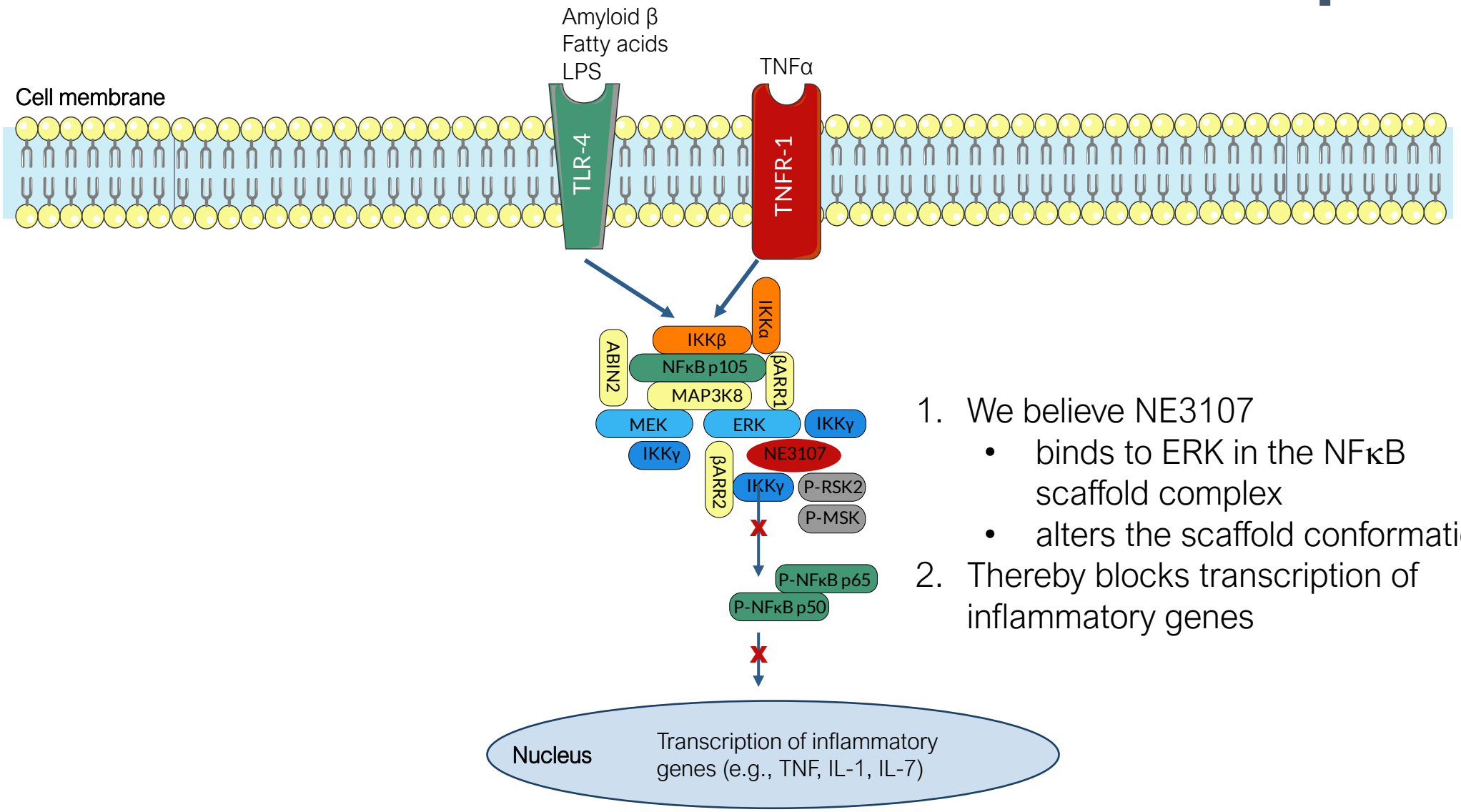
08 MAP3K8-dependent ERK phosphorylation of TNFR1

09 Internalization of the TNF/TNFR1 complex leading to further inflammatory signaling

# ERK plays a critical role in the NFκB scaffold complex

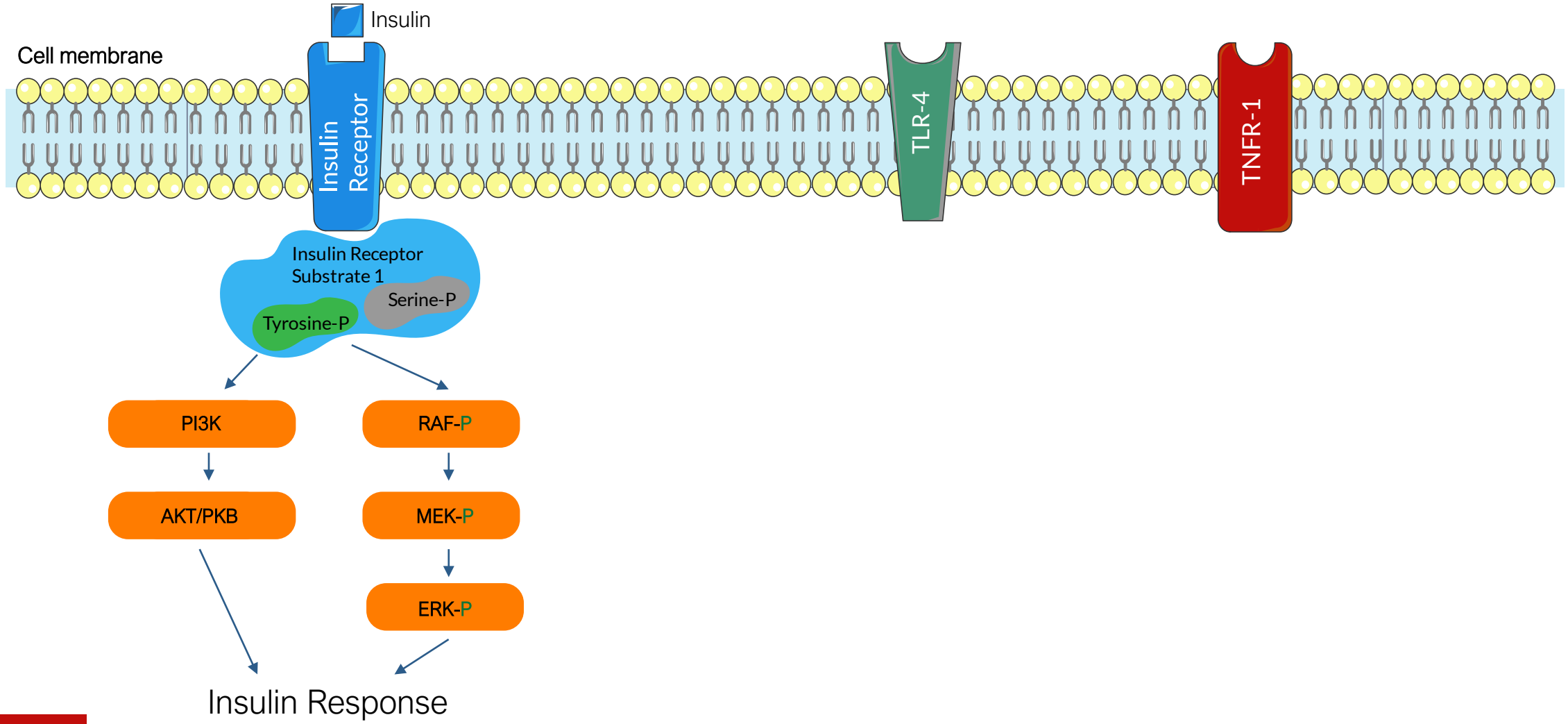


# We believe NE3107 alters the NFκB scaffold complex

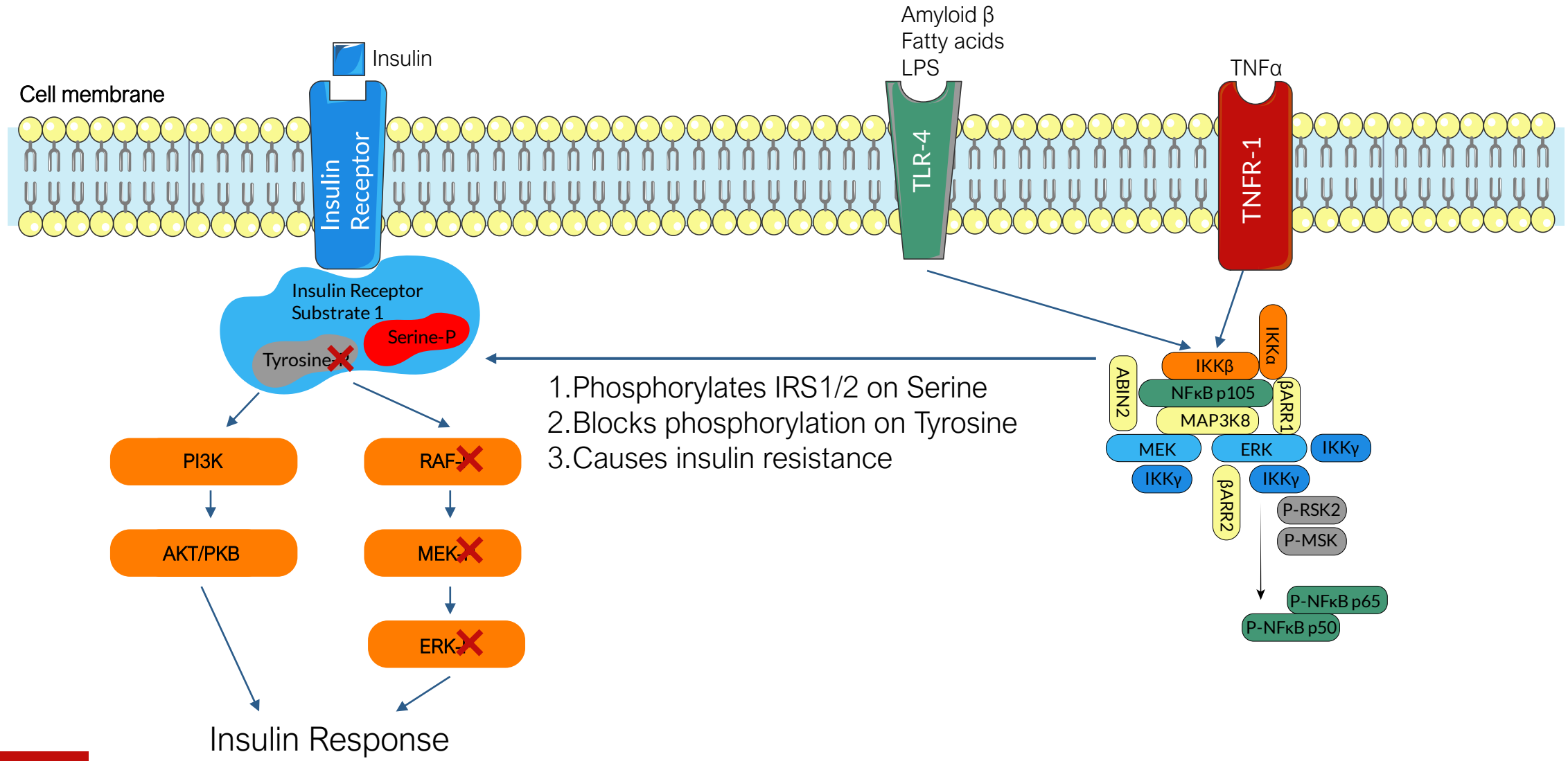



1. We believe NE3107
   - binds to ERK in the NFκB scaffold complex
   - alters the scaffold conformation
2. Thereby blocks transcription of inflammatory genes

# Normal insulin signaling



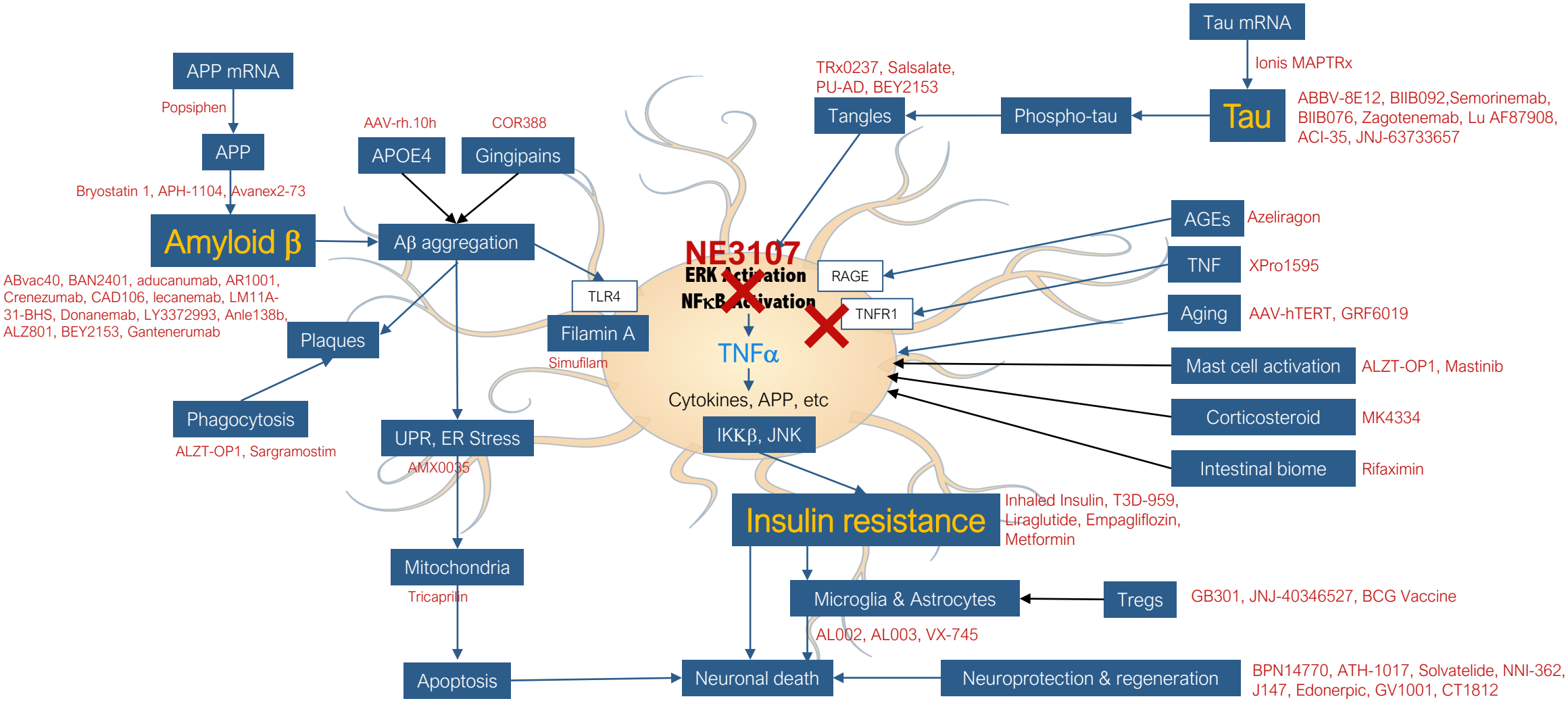
# Inflammation-mediated insulin resistance





# NE3107 believed to modulates inflammation at the central hub, thereby reducing downstream inflammatory cascade



# Expanding beyond NE3107

- HE3291 is a sister molecule with similar activity profile as NE3107
- We are resuming discovery research to explore additional molecules and indications
  - We now have a much better understanding of NE3107's presumed MOA
  - Enables even more precise medicinal chemistry to target binding sites
- Focus areas will be communicated in due course

# Alzheimer's Disease

# Alzheimer's Disease program overview

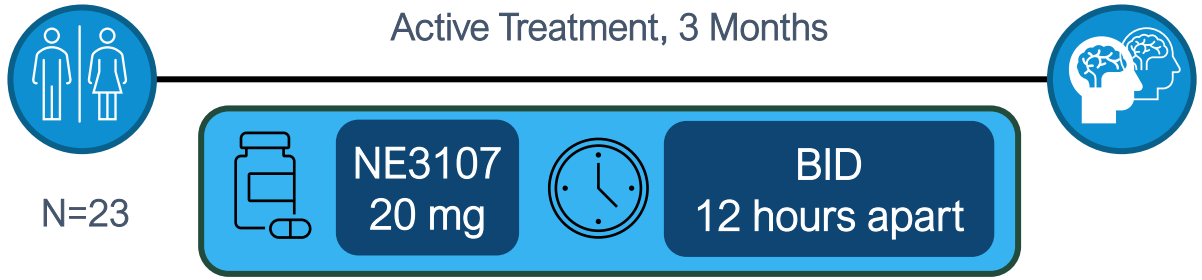
- Results from NE3107 Phase 2 exploratory biomarker trial in Mild Cognitive Impairment (MCI)/mild-AD reported at the CTAD Annual Conference in December 2022
  - First data set showing impact on cognition, p-tau, and imaging biomarkers
  - Impact on biological aging created new program on epigenetics & longevity
- NM101 Phase 3 in mild- to moderate-AD fully enrolled
  - Last patient visit expected in September 2023. Topline data readout expected October 2023
- Future clinical trials
  - Radiance-MCI 1 being launched by June 2023 to focus on US registration
  - Follow-on trials for global registrations in MCI and mild/moderate AD targeted for early 2024

# NE3107 Phase 2 exploratory biomarker trial

Open-Label Single-Arm 3-Month Study

**Inclusion criteria**
- 50-89 years old
- Cognitive decline due to dementia
- QDRS score: 1.5-12.5
- CDR score: 0.5 (MCI) or 1 (mild dementia)

**Exclusion criteria**
- Prior imaging inconsistent with AD
- History of stroke that resulted in cognitive or motor deficits
- MRI/CT evidence of moderate/large cerebral infract




**Change from baseline assessments**

| Neuroimaging | Clinical Assessments | Biomarker Assessments |
|---|---|---|
| MRS | MMSE | Plasma TNF-α |
| Relative CBF | ADAS-Cog12 | CSF Aβ42 |
| Anatomical imaging | MoCA | CSF p-tau |
| BOLD imaging* | QDRS and CDR | P-tau:Aβ42 ratio |
| DTI-NODDI† | ADCOMS | Brain glutathione (by MRS) |

*Preliminary data; †Data analysis ongoing.
ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS, AD Composite Score; ASL, arterial spin labeling; BID, twice per day; BOLD, blood-oxygen level dependent; CBR, cerebral blood flow; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; DTI-NODDI, diffusion tensor imaging – neurite orientation dispersion and density imaging; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRS, magnetic resonance spectroscopy; NMR, nuclear magnetic resonance; QDRS, Quick Dementia Rating Scale.

# Clinical outcomes assessments

## NE3107 Was Associated With Improvements From Baseline in Clinical Outcomes of Neuropsychological and Cognitive Assessments after 3 months of Treatment

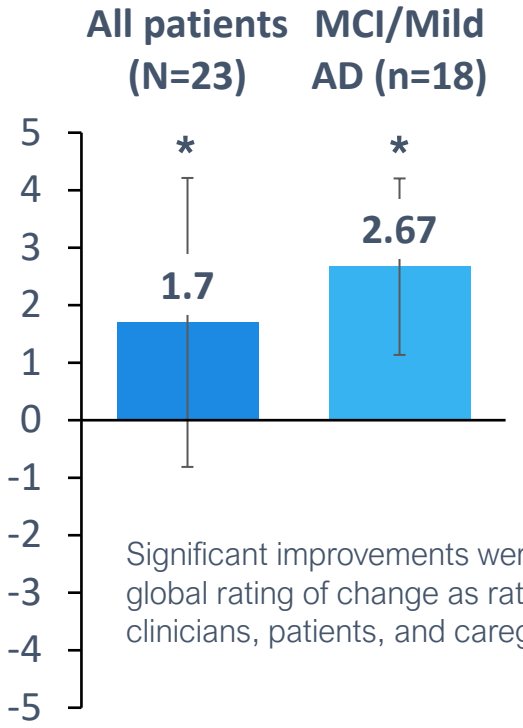
### Changes from Baseline in Clinical Assessments

| Assessment | All Patients (N=23) | MCI/Mild AD (n=18) |
|---|---|---|
| ADAS-Cog12 | −0.913 | **−2.167*** |
| MMSE | −0.74 | −0.39 |
| MoCA | −0.04 | 0.56 |
| QDRS | −0.54 | **−1.56*** |
| CDR | 0.04 | **−0.11*** |
| ADCOMS | 0.0049 | **−0.07*** |

In the patients with baseline MMSE ≥20 (indicating MCI or mild dementia), NE3107 was associated with statistically significantly improved cognitive functioning vs baseline, in ADAS-Cog12, QDRS, CDR, ADCOMS,

Green=Improvement

### Clinician-Rated Global Rating of Change




Significant improvements were seen in global rating of change as rated by clinicians, patients, and caregivers

*$p<0.05$

# Biomarker improvements

## Changes from baseline in biomarkers

| Assessment | All Patients (N=23) | MCI/Mild AD (n=18) |
|---|---|---|
| TNF-α, pg/mL | –0.452 | –0.563 |
| CSF p-tau, pg/mL | –1.1 | **–1.66*** |
| P-tau:Aβ42 ratio | –0.0033 | **–0.0024*** |

In the MMSE ≥20 patients, NE3107 was associated with statistically significant improvements in p-tau and the p-tau:Aβ42 ratio

## Correlations between biomarkers and clinical outcomes

| | All Patients | MMSE ≥20 n=18 |
|---|---|---|
| **ADAS-Cog12** | | |
| TNF-α | r=0.46 | **r=0.59*** |
| **ADCOMS** | | |
| Aβ42 | **r=0.53*** | r=0.31 |
| P-tau | **r=0.49*** | r=0.37 |

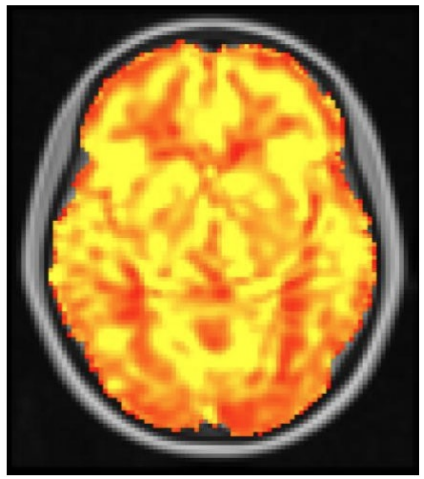
NE3107 was associated with statistically significant correlations between several clinical assessments and biomarkers

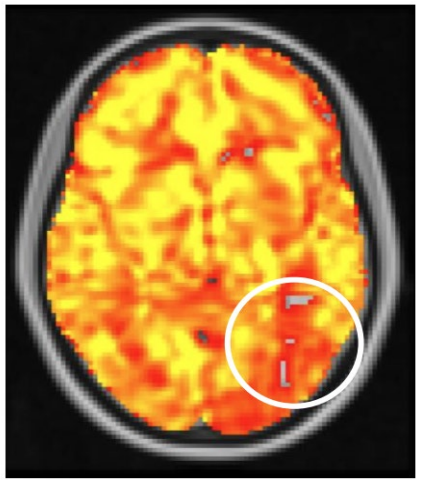
Green=Improvement

*$p<0.05$

# Neuroimaging methodology

- Functional MRI data were submitted to blinded review and scoring by two independent clinician-readers. Inter-rater reliability was 96%; in the event of disagreement between raters, data were subjected to additional review and ultimately scored by consensus
- Criteria for “Improved,” “Stable,” or “Declined”
  - Improved: No longer meets criteria for abnormality
  - Declined: Previously ‘normal’ scan met criteria for abnormality at follow-up OR ▪ Abnormality becomes more extensive in an abnormal patient
  - Stable: No significant change between baseline and follow-up scans



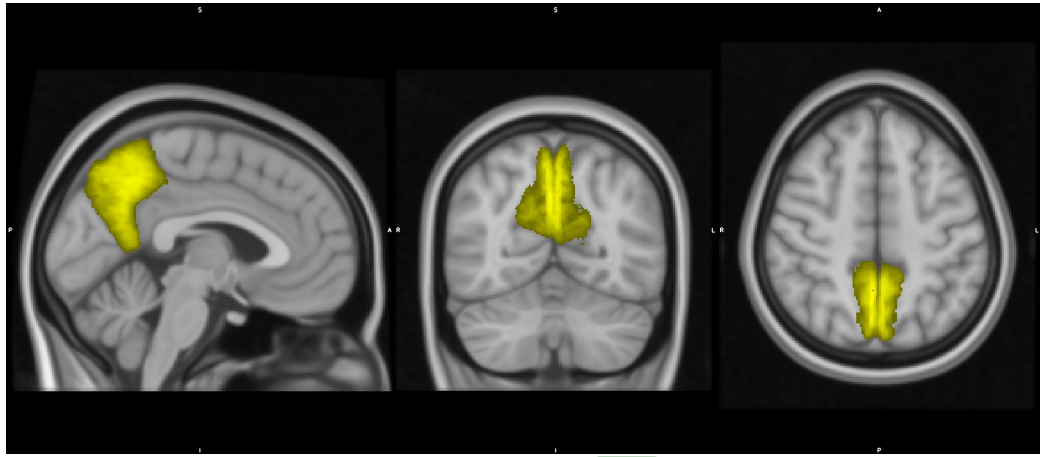


**Criteria for Abnormality:** Perfusion / Relative cerebral blood flow (CBF): 30% decrease in signal intensity in the temporal, parietal, or occipital lobes (in at least one hemisphere) was scored as abnormal.

Examples shows a subject that had decreased perfusion (abnormal) that improved at follow-up

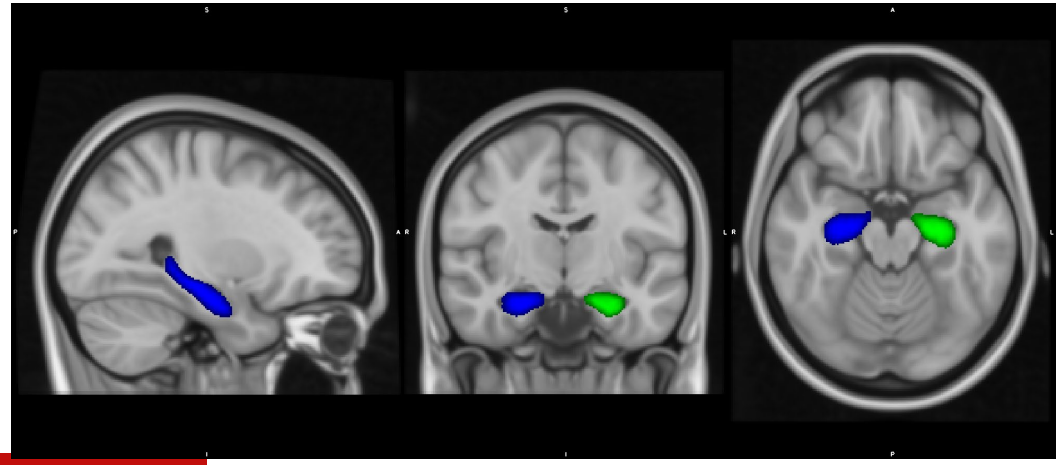
# NE3107 increased functional connectivity from baseline in group analysis using BOLD imaging

Precuneus ROI

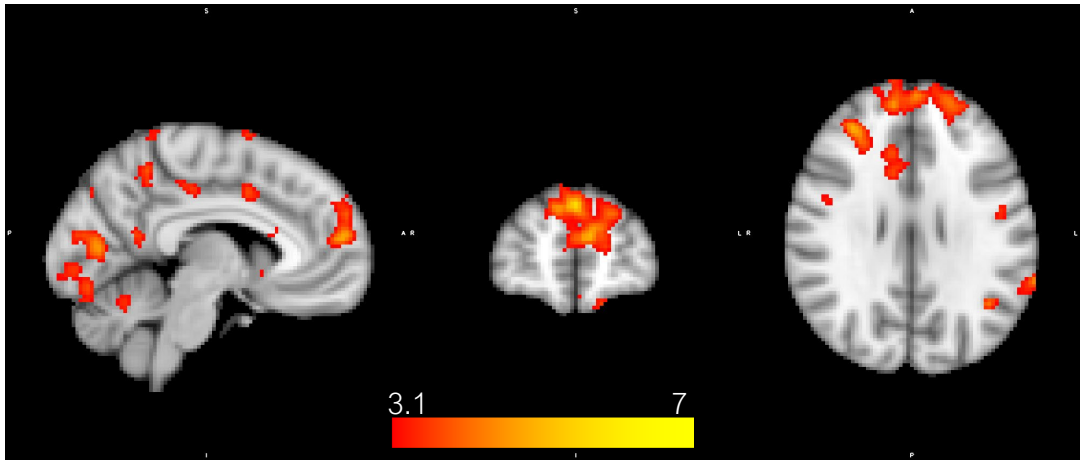


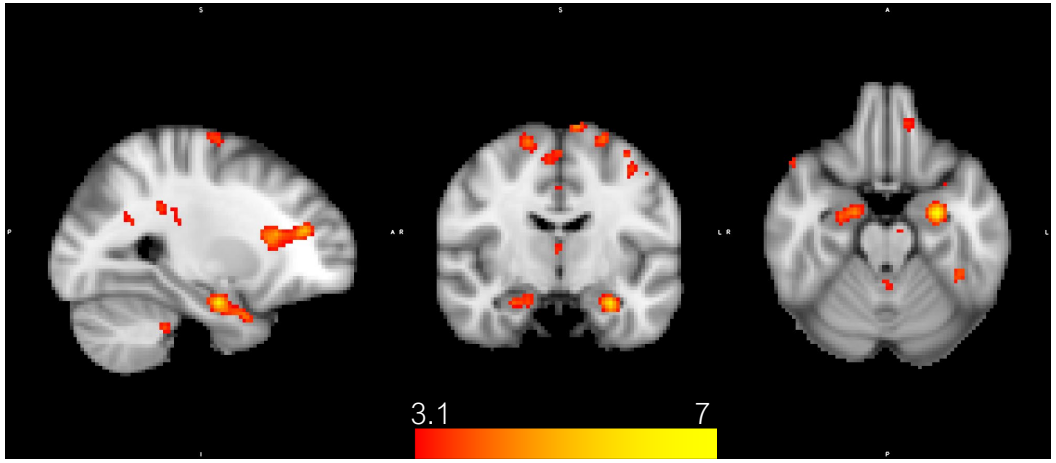
Right HC ROI

Left HC ROI



Statistically significant regions of increased connectivity



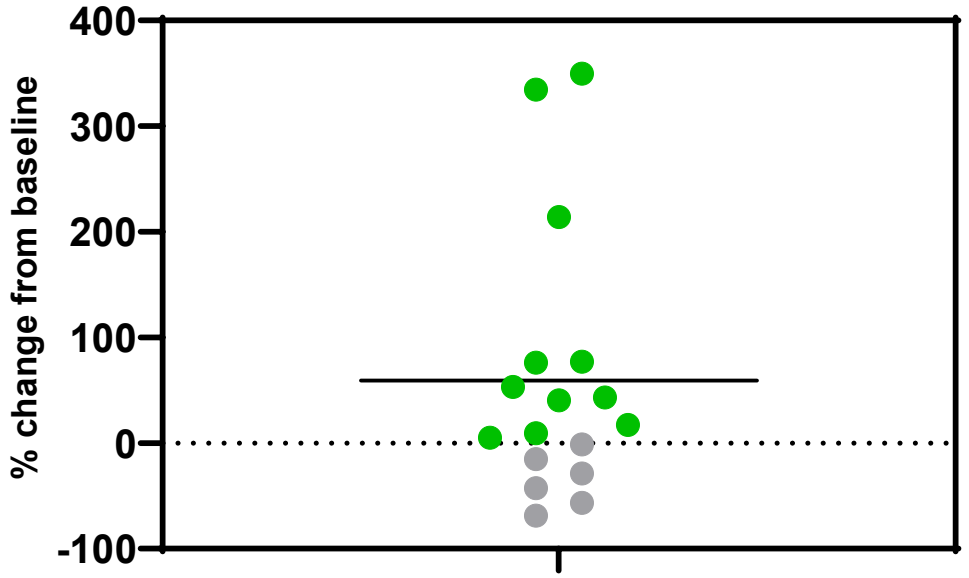





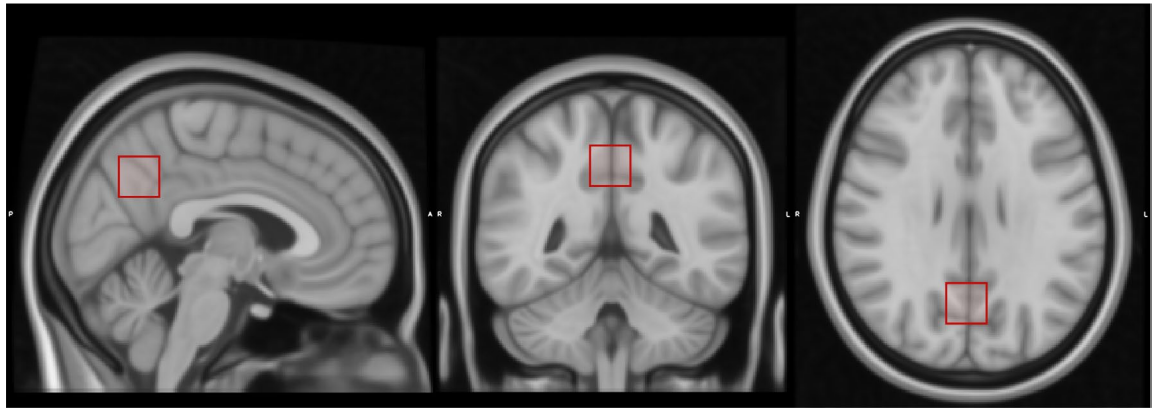

 

# NE3107 associated with reduced oxidative stress in the brain

Brain glutathione assessed by MRS of Precuneus




**11/17 (59%) improved**
**mean +59% change**
**P=0.069**



Significant correlation of Glutathione with:
TNF-α (r=−0.44)
ADAS-Cog12 (r=−0.45)

# Update on NM101 Phase 3 in Mild/Moderate

- Trial fully enrolled as of February 28, 2023
  - 100 patients completed treatment at that time
  - Top-line data readout expected in October 2023
- Trial continues to have a good safety profile and low discontinuation rate
- Blinded baseline data shows evidence of metabolic inflammation in amyloid β positive and negative, and APOEε4 positive and negative subjects submitted for presentation at the American Diabetes Association's 83rd Scientific Sessions in San Diego, June 23-26, 2023

# Radiance-MCI 1 Trial

- A potentially pivotal Phase 2/3, double-blind, randomized, placebo-controlled, parallel group, multicenter study of NE3107 in MCI subjects
  - MCI patients have a measurable loss of memory, but have not yet shown significant functional impairment
  - MCI is defined by Stage 2 and Stage 3 diagnostic criteria in Draft Guidance for Industry- Early AD: Developing Drugs for Treatment (February 2018)
  - Most patients with MCI continue to degenerate to AD. Inflammation drives both conditions
  - Arresting/reversing at the MCI stage (CDR less than 0.5) has the potential for the greatest long term patient benefit
- Patients 50-80 years old qualify with computer-based tests of cognitive impairment
- Patients will receive 20 mg NE3107 or placebo for 6 months for CDR-SB primary endpoint
  - Patients randomized to NE3107 will continue receiving drug for 1 year to observe effect on disease progression
  - Patients randomized to placebo at the start crosses over to NE3107 for 6 months (delayed start)
- Anticipate first patient enrollment by June 2023
- Trial approach provides maximum flexibility to work with FDA for approval
  - Single MCI trial in combination with mild-/moderate-AD Phase 3 for full approval in MCI in the US
  - A second MCI trial to be started in 2024 for as second trial for full approval in MCI globally

# Parkinson’s Disease

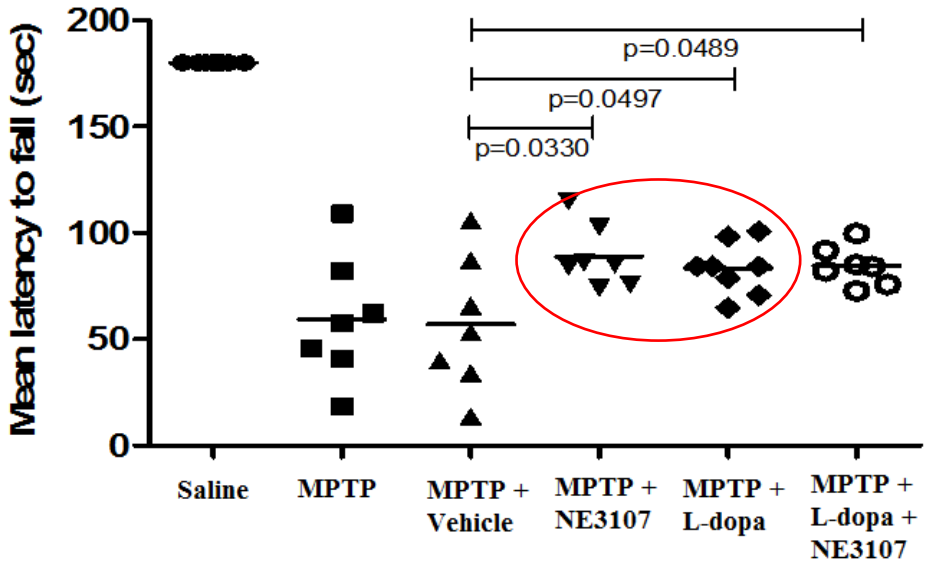
# Parkinson's Disease program overview

- Clinical development was initiated based on strong data from preclinical studies
- Phase 2 NM201 trial launched with 2 main objectives
  - Primary: safety and drug-drug-interaction study (as requested by FDA) to demonstrate the absence of adverse interactions with levodopa
  - Secondary: detect efficacy signal in humans
  - Small study not powered for statistical significance
- NM201 objectives were both met
  - 3+ points greater motor control vs. placebo on the UPDRS Part 3 score. 6+ point among <70 years old
  - Statistically significant fraction of patients experienced morning "on" state with levodopa withheld overnight and prior to receiving their morning medication
- Clinical studies in levodopa naïve patients being launched
  - SUNRISE-1 is a potentially pivotal Phase 2b starting 3Q2023
  - SUNRISE-2 is a potentially pivotal Phase 3 starting late 1Q2024

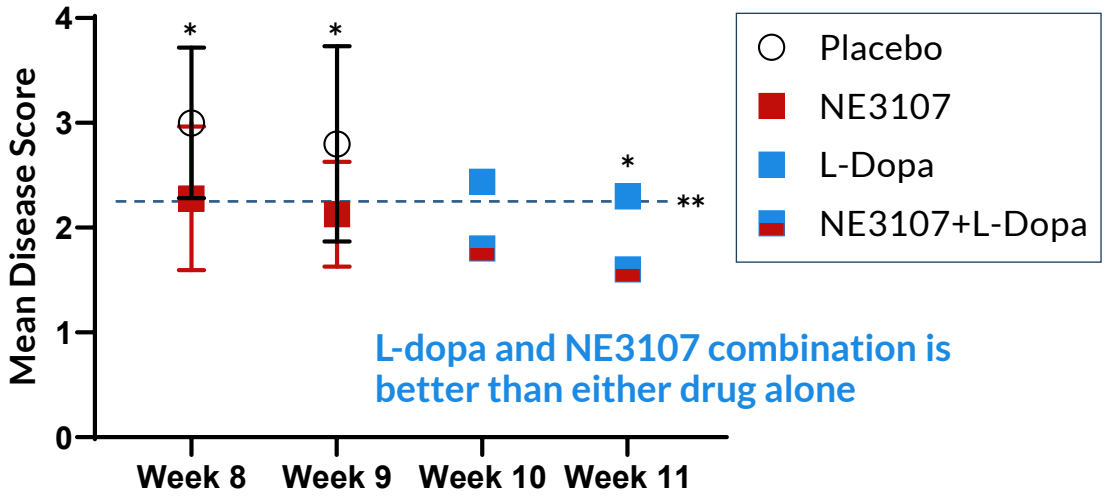
# NE3107 has similar promotoric activity to L-dopa in rodent* and marmoset* models

Funded by
THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

## MPTP Mouse




## MPTP Marmoset treated at Week 8




**L-dopa and NE3107 combination is better than either drug alone**

*p<0.001 compared to other treatment arm in time period
** L-Dopa at week 11 not statistically different from NE3107 at weeks 8 and 9

**NE3107's promotoric effects observed within 4 days of treatment**

* Funded by MJFF for Parkinson's Research, MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a toxin used to mimic many aspects of PD

# NE3107 decreases L-Dopa-induced dyskinesia (LID) in marmosets*

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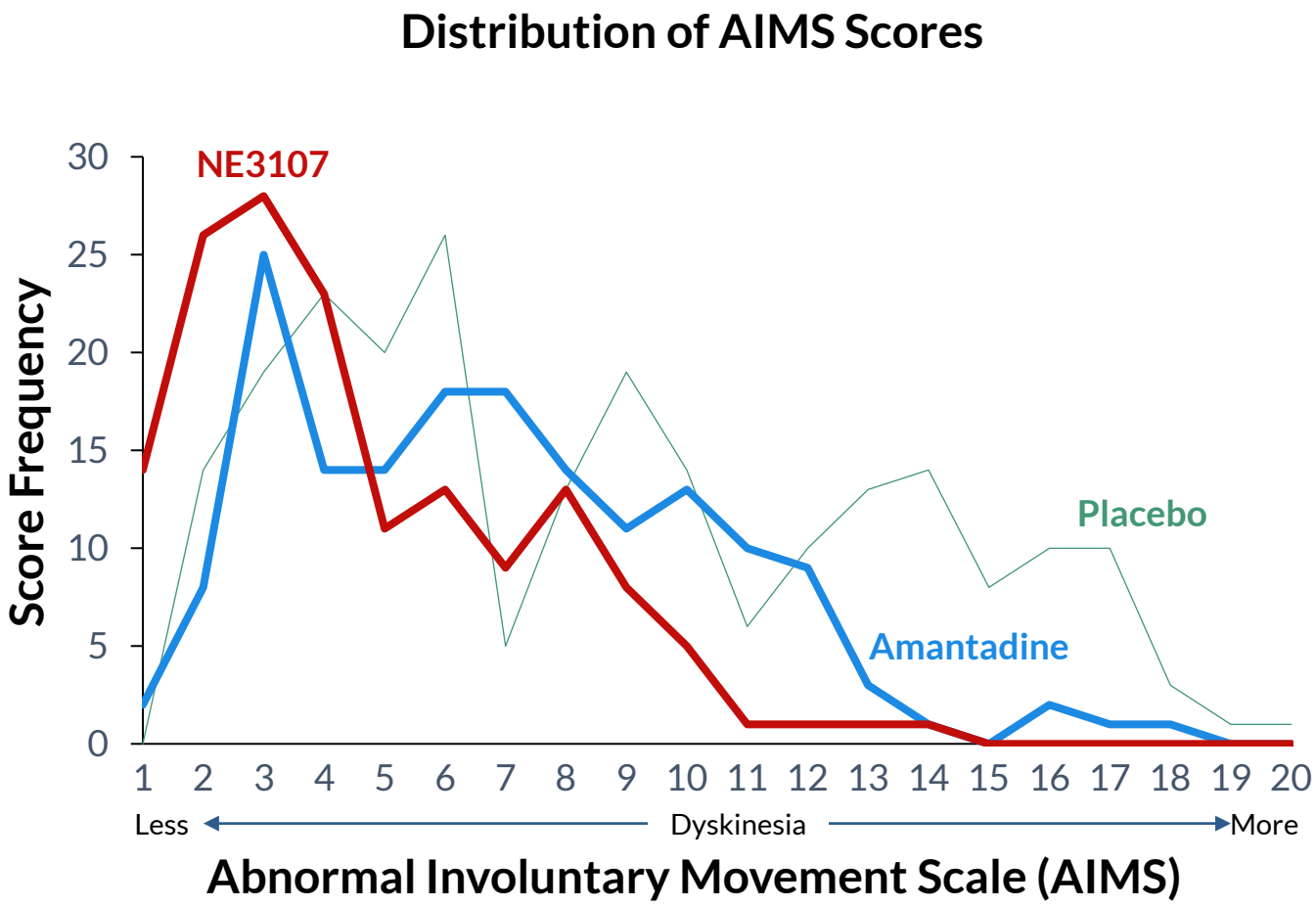


* Funded by MJFF for Parkinson's Research

# NE3107 preserved ~2X TH+ (dopaminergic) neurons in MPTP marmosets*

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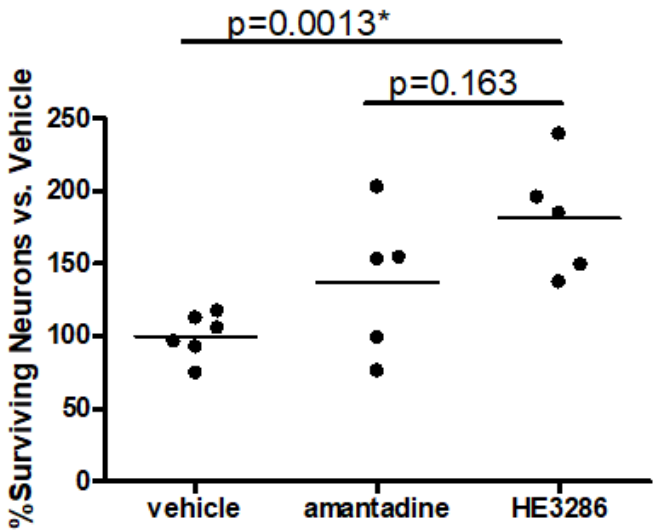
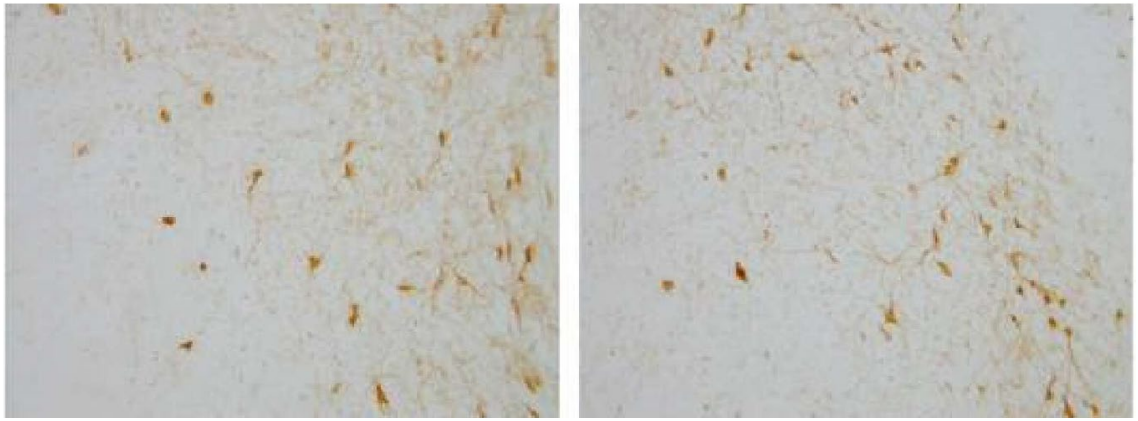
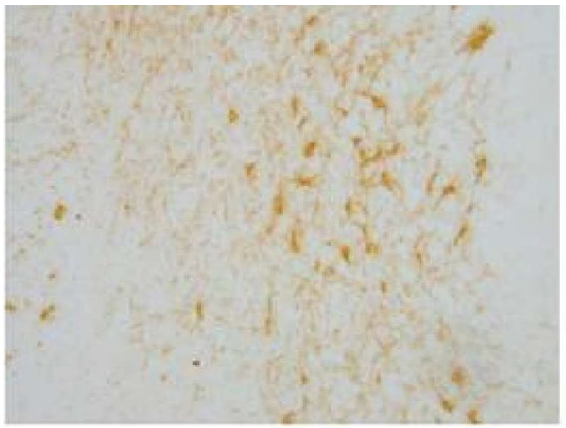


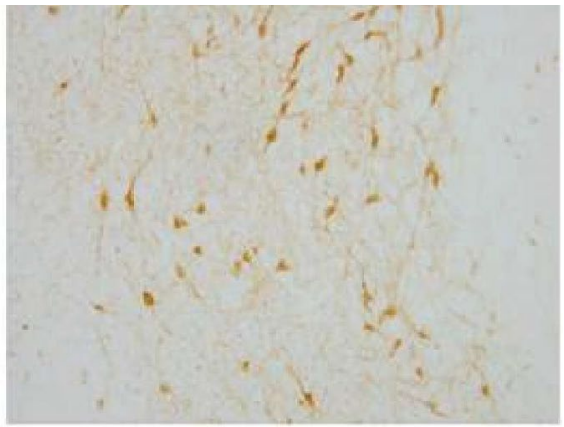

Control moneys (M09100 and M11008)



HE3286 (M11007)



Amantadine (M10084)



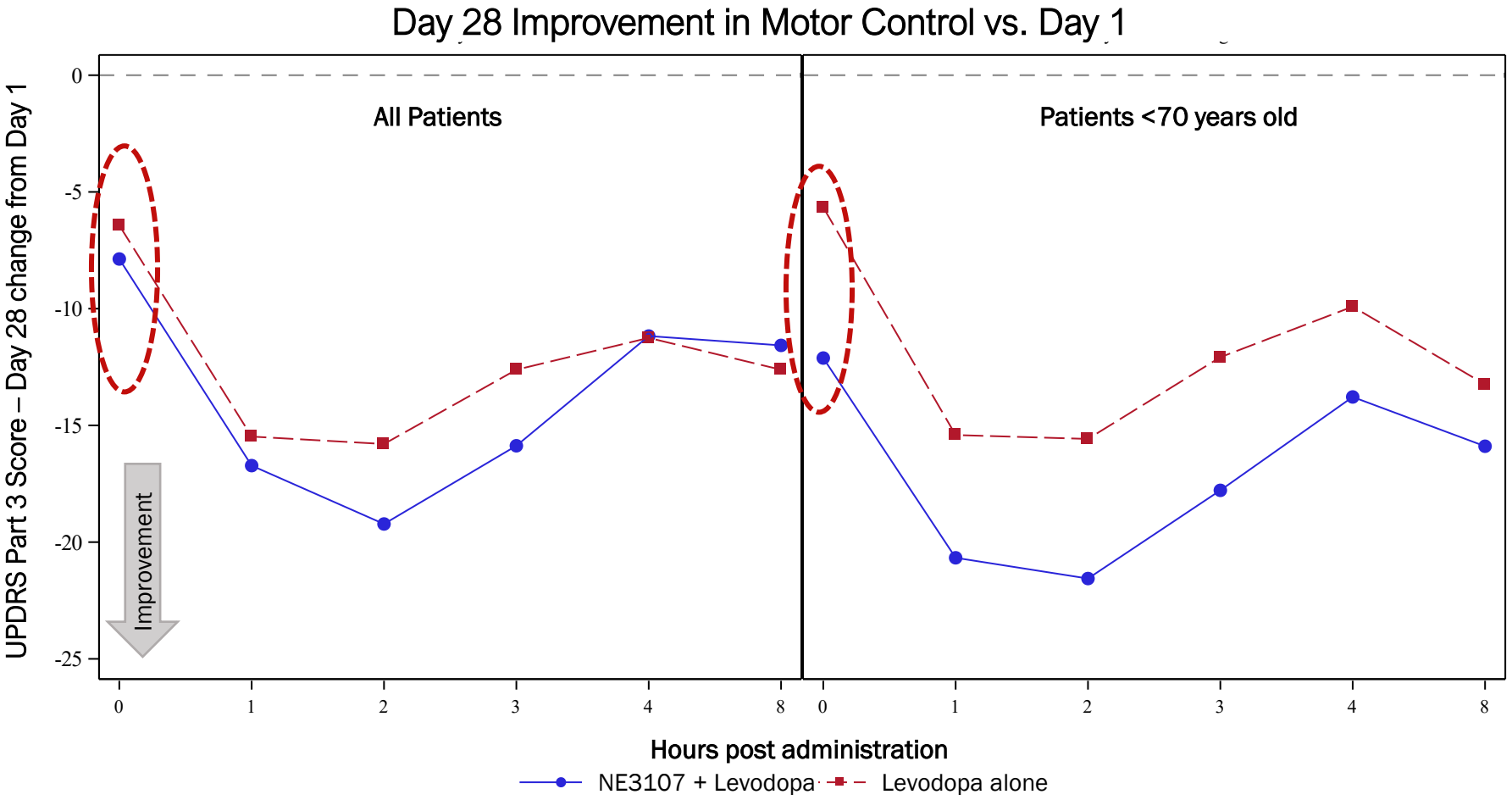
Note: NE3107 was originally known as HE3286 from Hollis Eden Pharmaceuticals, *Funded by MJFF for Parkinson's Research

# Parkinson's disease clinical development program

- NM201 sought to satisfy FDA requirement for drug-drug interaction (DDI) study with L-Dopa and assess NE3107 promotoric and anti-LID activity
- 45 patients with defined L-Dopa "off state" randomized 1:1 active:placebo, 20 mg BID for 28 days
- Primary endpoints: Safety, L-Dopa PK and DDI
- Secondary endpoint: MDS-UPDRS* part 1-3 and NMSS**

* Movement Disorder Society-Unified Parkinson's Disease Rating Scale
** Non-Motor Assessment Scale for Parkinson's Disease

# NE3107-treatment patients experienced fewer motor symptoms before morning drug administration

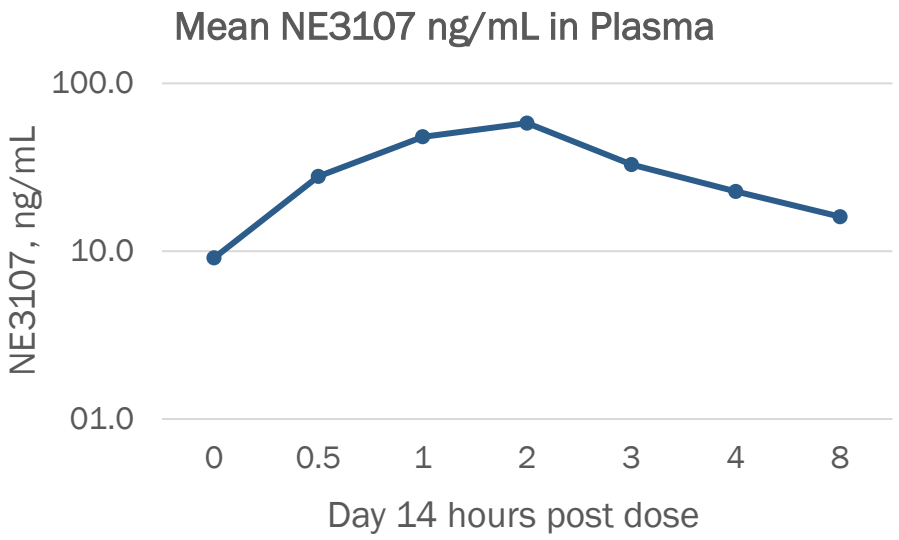


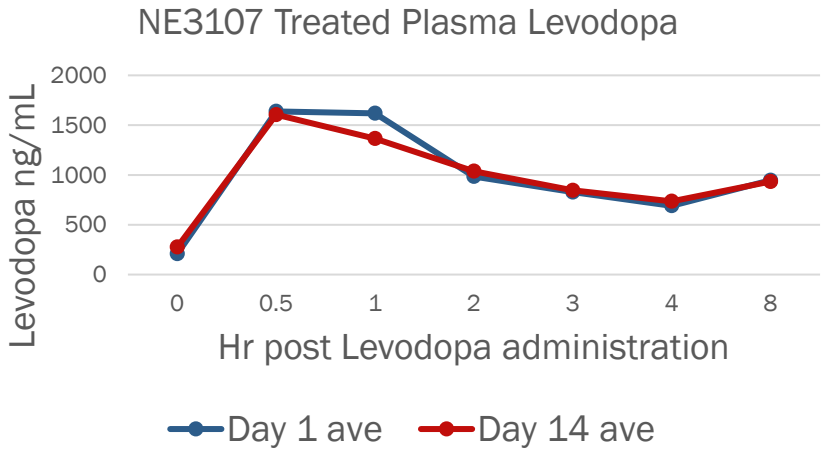

| | NE3107 | Placebo |
|---|---|---|
| "On" at t=0 | 6 | 0 |
| Total patients | 20 | 19 |
| P-value* | 0.02 | |

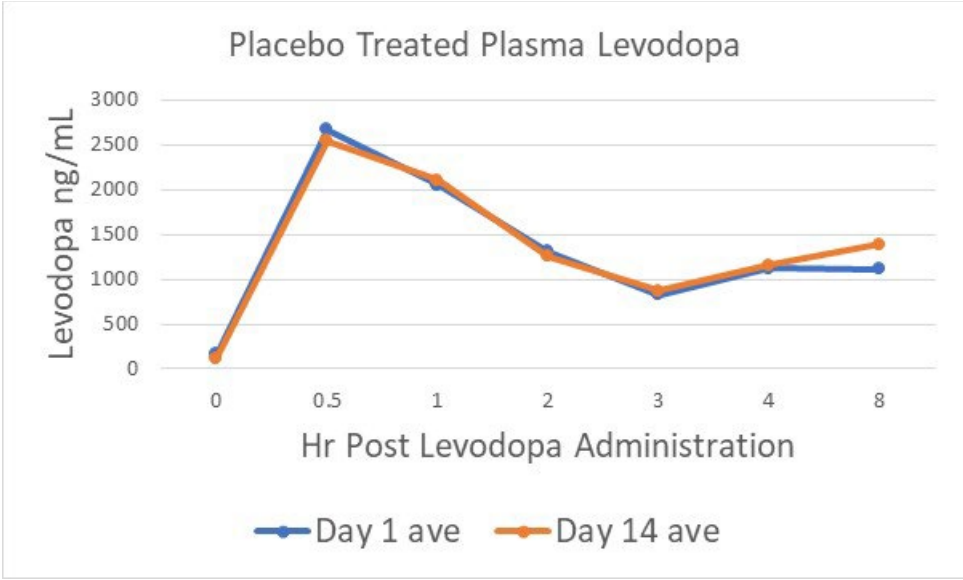
* Fisher's exact test

# Desirable pharmacokinetics – no observed DDI

0-8 hr 231 ngh/mL (SD 22.38)



# Collaboration with Parkinson Study Group


- The largest, pro-active, not-for-profit scientific network of Parkinson Centers in North America for over 30 years
- Strict credentialing process, with over 150 Credentialed PSG Centers in North America, Hawaii, and the Caribbean
- Over 350 credentialed investigators and 245 coordinators and growing
- Strong partnerships with both the **Michael J Fox Foundation** and the **Parkinson's Foundation**
- International collaborations in India, China, Scandinavia, & Germany
- Partners receive support from credentialed coordination & biostatistics centers: **CTCC** at the University of Rochester, **NCRI** at Massachusetts General Hospital, and the **Columbia University Biostatistics Center**

# BioVie's Parkinson's Advisory Committee

- **Anthony Lang** (co-chair), MD.  Author of 950+ peer-reviewed papers and 100+ book chapters in Parkinson's Disease
  - Director, the Morton and Gloria Shulman Movement Disorders Clinic at Toronto Western Hospital
  - Jack Clark Chair for Parkinson's Disease Research at the University of Toronto
  - Lily Safra Chair in Movement Disorders at the University Health Network in Toronto
  - Director, the University Health Network and the University of Toronto Edmond J. Safra Program in Parkinson's Disease
  - Director, Division of Neurology at the University of Toronto
- **Hubert Fernandez** (co-chair), MD. Director, Center for Neurological Restoration, Cleveland Clinic
- **Tanya Simuni**, MD, FAAN. Arthur C. Nielsen Jr Professor of Neurology and the Director of the Parkinson's disease and Movement Disorders Center at Northwestern University Feinberg School of Medicine
- **Rajesh Pahwa**, MD. Laverne and Joyce Rider Professor of Neurology, chief of the Parkinson's and Movement Disorder Division and director of Parkinson Foundation Center of Excellence at the University of Kansas Medical Center
- **Sheng Luo**, PhD. Professor of Biostatistics & Bioinformatics, Duke University

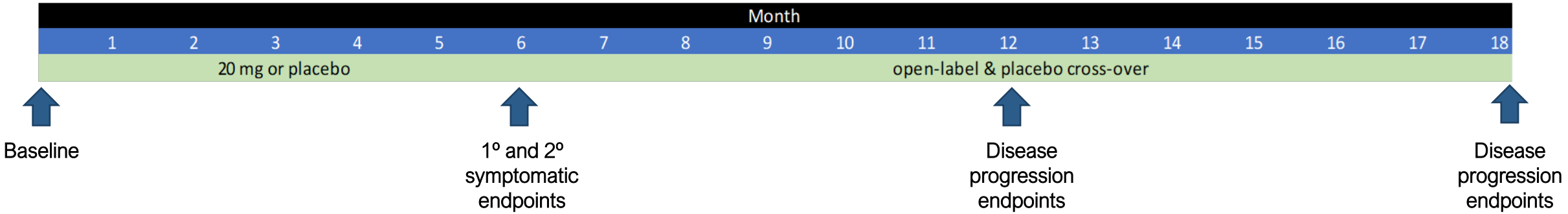
# Strong support from advisors for a more aggressive plan to address significant unmet medical needs

*"The Parkinson's Study Group (PSG) has provided guidance to many industry partners who have successfully brought to market Parkinson's therapeutics that address the unmet needs of patients.* ***The PSG members unanimously recommended that the company accelerate plans to explore the potential efficacy of NE3107 in levodopa naïve Parkinson's patients due to the current unmet need.*** *With great enthusiasm, the PSG advisory members look forward to collaborating with BioVie and seeing the results of clinical trials in this patient population"*

Dr. Hubert Fernandez on behalf of the Parkinson's Study Group,
Co-Chair PSG and Director of the Center for Neurological Restoration at Cleveland Clinic

March 15, 2023

# SUNRISE 1 and 2 in Treatment Naïve PD Patients




- SUNRISE-1 and Sunrise-2 have the same design in levodopa naïve PD patients
- 20 mg NE3107 or placebo BID, rescue medication permitted as directed by the investigator
- 6-month to primary endpoint (UPDRS Part 3 score) and secondary endpoint PADLS*
  - Placebo-cross over to NE3107 for 12-month extension to demonstrate disease modification
- Sunrise-1 to enroll 100 patients randomized 1:1, first patient enrollment 3Q2023
  - Blinded interim at 3 months to repower if needed
- Sunrise-2 expected to enroll an estimated 200 patients (to be repowered from Sunrise-1)
  - Start late 1Q2024 with primary endpoint readout 3Q2025
  - Sunrise-1 results in 3Q2024 will be used to re-power SUNRISE-2 Phase 3, if necessary

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* Parkinson's Disease Activities of Daily Living Scale, a patient reported outcome

# Additional endpoints

## Secondary endpoints

- Parkinson's Disease Activities of Daily Living Scale* (PADLS)
- Time to initiation of PD therapy
- Parkinson's sleep scale

## Exploratory endpoints

- Rate of disease progression defined by:
- Change in MDS-UPDRS Part 3 score compared to baseline after withholding all PD and study medications for 24 hours in treatment compared to placebo groups at 26, 52, and 56 weeks
- Change in MDS-UPDRS Part 3 score compared to baseline after withholding all PD and study medications for 24 hours in NE3107 patients after 26 and 52 weeks of treatment compared to historical controls, and at week 56
- Plasma levels of inflammatory biomarkers (adiponectin, leptin, CRP, ceruloplasmin, C1q, IFNγ, IL1β, IL6, IL17, IL23, MCP1, RANTES, and TNFα)
- Change in heart rate variability compared to baseline
- Changes in DNA methylation compared to baseline

*Patient reported outcome

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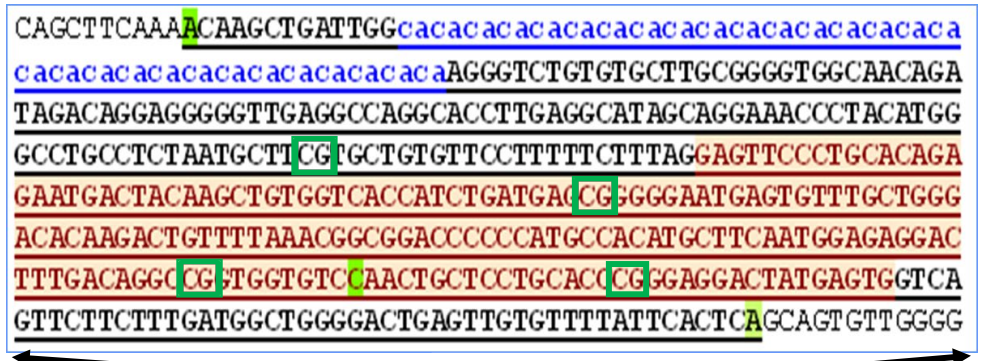
# Epigenetics & Longevity

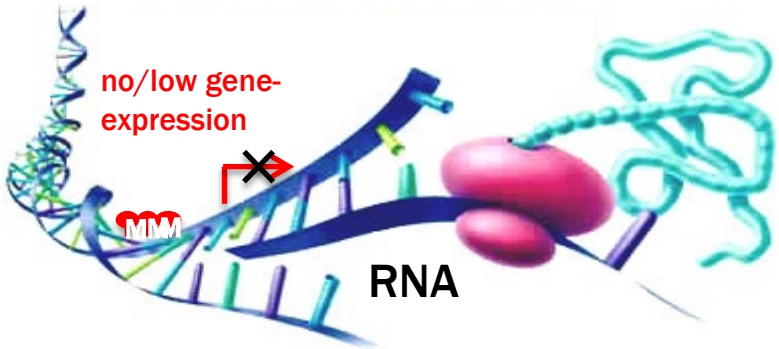
# Epigenetics & Longevity program overview

- Early stages of program initiated based on early findings that NE3107 may affect the biological aging process
- We have identified the nucleus of academic collaborators to steer this program
  - Ekaterina Rogaeva, Ph.D., Professor, Department of Medicine University of Toronto;  Chair Research on Dementia with Lewy Bodies; Tanz Center for Research in Neurodegenerative Diseases.
  - Nikolaos Daskalakis Ph.D., M.D., Assist. Prof. Psychiatry; Director Neurogenomics and Translational Bioinformatics Lab, McLean Hospital, Harvard Medical School

# Genome reacts to environment, mutations & aging: epigenetics




- 25,000 genes
- 6 billion base pairs
- 4% code for proteins
- 100 million variations



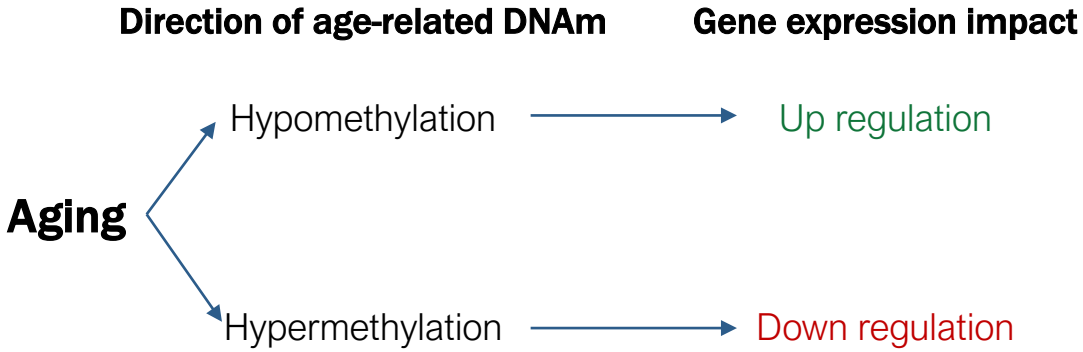

**Protein**

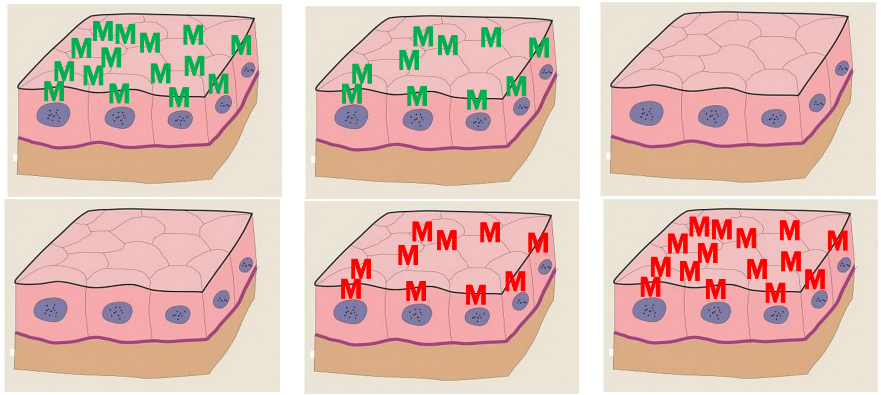
## DNAm controls gene-expression

- 28 million CpGs in genome
- DNAm arrays: <1 million CpGs
- DNAm levels at some CpGs are age-related, affecting expression of >2000 genes

- Diet and exercise remains the most accepted tool for influencing epigenetics
- Clinicians have experimented with metformin and rapomycin

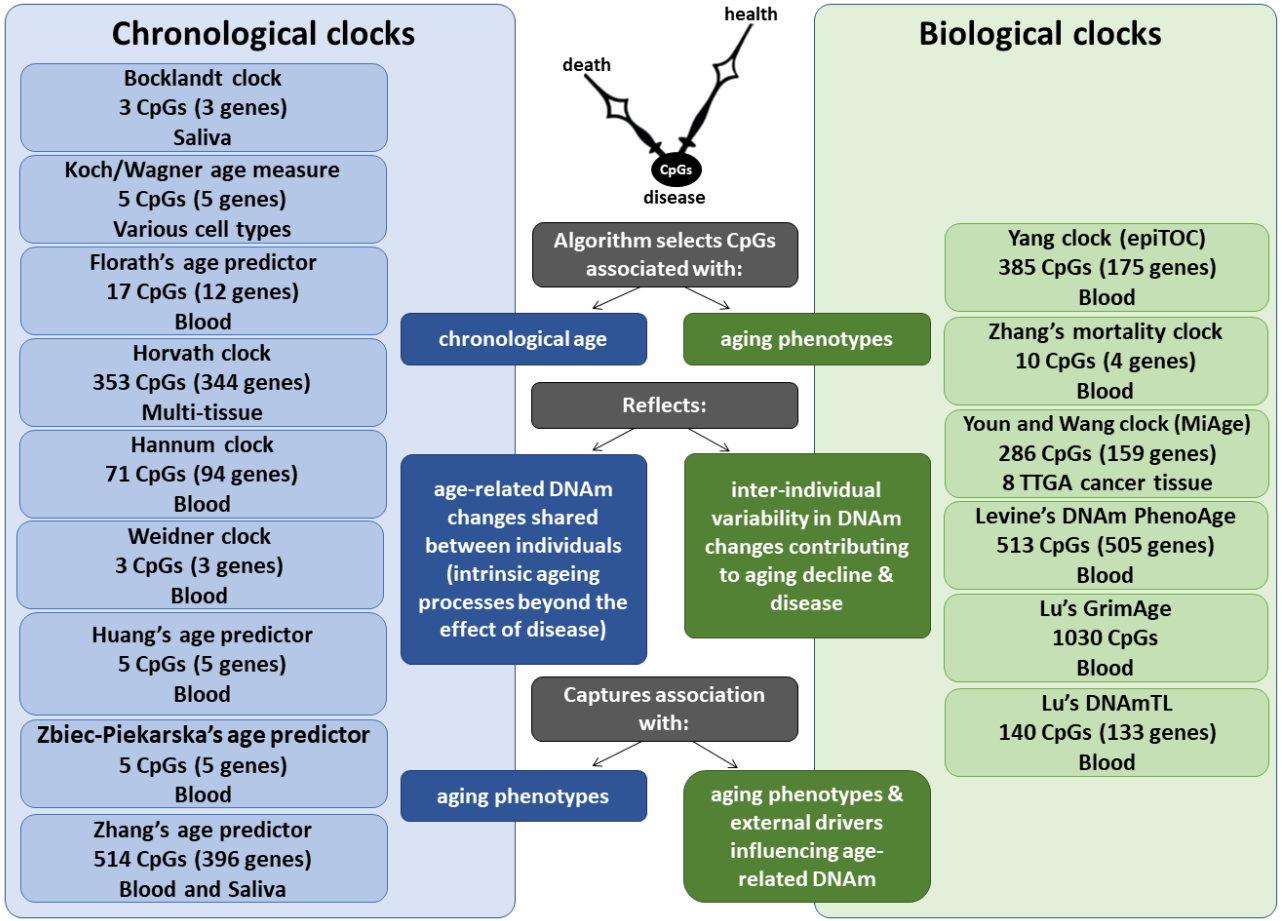
# DNA methylation clocks and their predictive capacity for aging phenotypes and health span



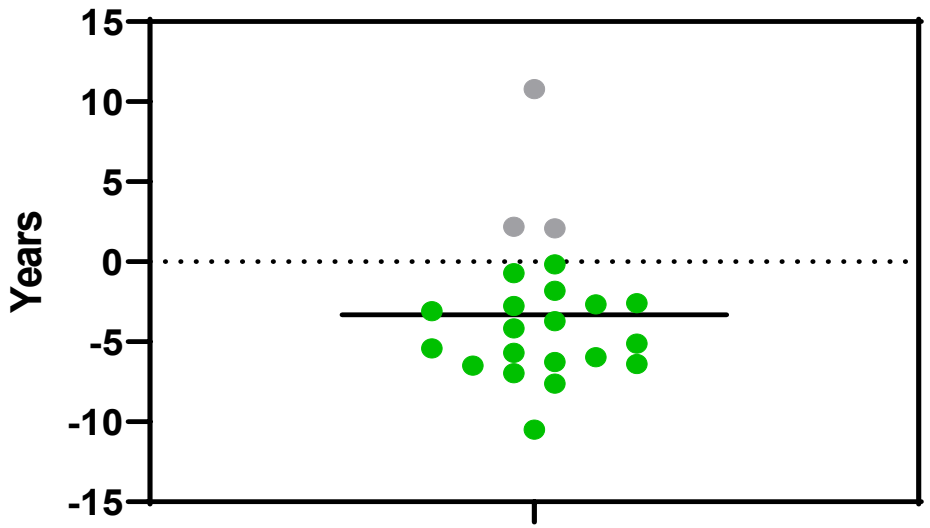
- DNAm clocks are based on cumulative assessment of the methylation levels of many age-related CpGs
- DNAm clocks reflect biological aging, the pace of which varies among individuals
- 15 reported DNAm clocks reflect different mechanisms of aging

# Each DNAm clock is built according to a unique training method



# NE3107 decreased biological age in MCI/AD subjects

- Dr. Steve Horvath* developed an extremely precise Biological age DNA methylation clock, the **DNAmSkinBloodAge**
- The biological clock age was in close agreement with the chronological age (72.3 vs 71.6; +0.98%) at baseline
- After 3 months treatment with NE3107 there was a decrease in DNA methylation commensurate with 3.3 years reduction on the Skin Blood Clock (68.1 vs 71.6; -4.9%)




**mean -3.3 Years**
**95% CI -5.28 to -1.35**
**p=0.002**
**19/22 (86%) decreased**

* Professor of Human Genetics at the UCLA David Geffen School of Medicine and Professor of Human Genetics & Biostatistics at the UCLA Field School of Public Health

# Next steps

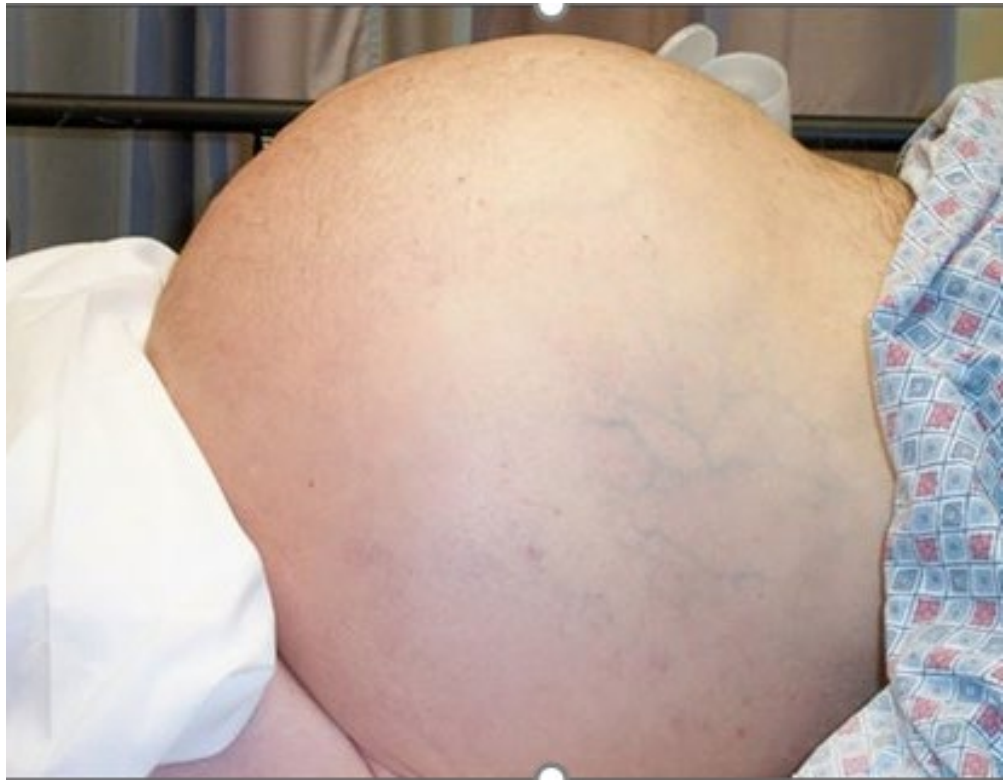
- Additional results of NE3107 modulation of DNA methylation pertaining to immunomodulatory cells, endocrine mediator expression, and their correlates will be presented at the Alzheimer's Association International Conference (AAIC) July 16-20, 2023

- Along with Drs. Rogaeva and Daskalakis, we are assembling longevity advisors, collaborators and team
  - To deepen Biovie's current epigenetic analyses in three diseases of aging: MCI, Mild-moderate AD, and PD
  - To broaden to additional areas of exploration

# Liver Disease

# Refractory Ascites

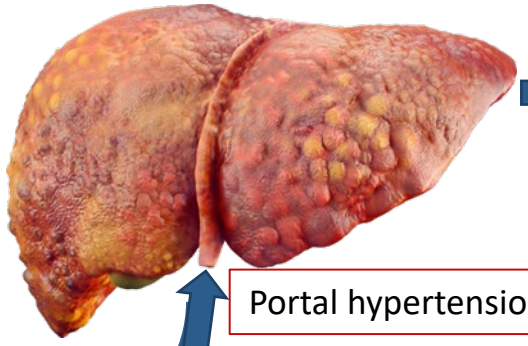
- Fluid build-up in the abdomen of patients with advanced cirrhosis
  - Cannot be controlled with an effective dose of diuretics
- No approved pharmacological treatments – unmet need
- First line treatment is repeated mechanical draining by paracentesis
  - Surgically implanted shunts an option in select patients
- Mortality > 40% in 12 months*



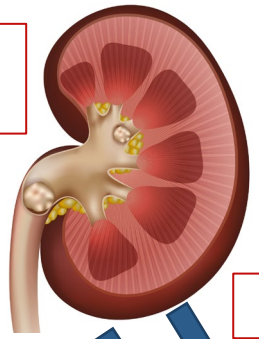
Very poor quality of life
Not typically hospitalized

* 1 Will et al. Dig Liver Dis. 2022 Aug;54(8):1007-1014.

# Ascites Pathophysiology



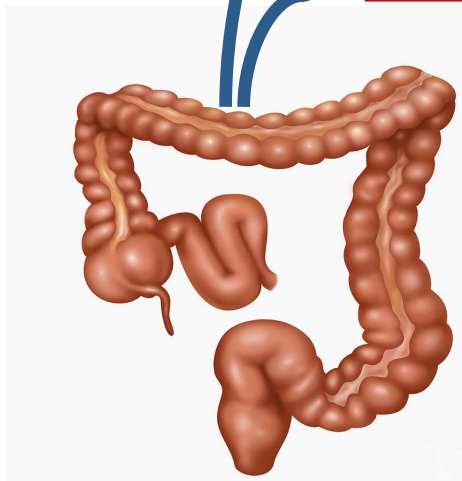
Decreased aldosterone metabolism



Retention of salt and water

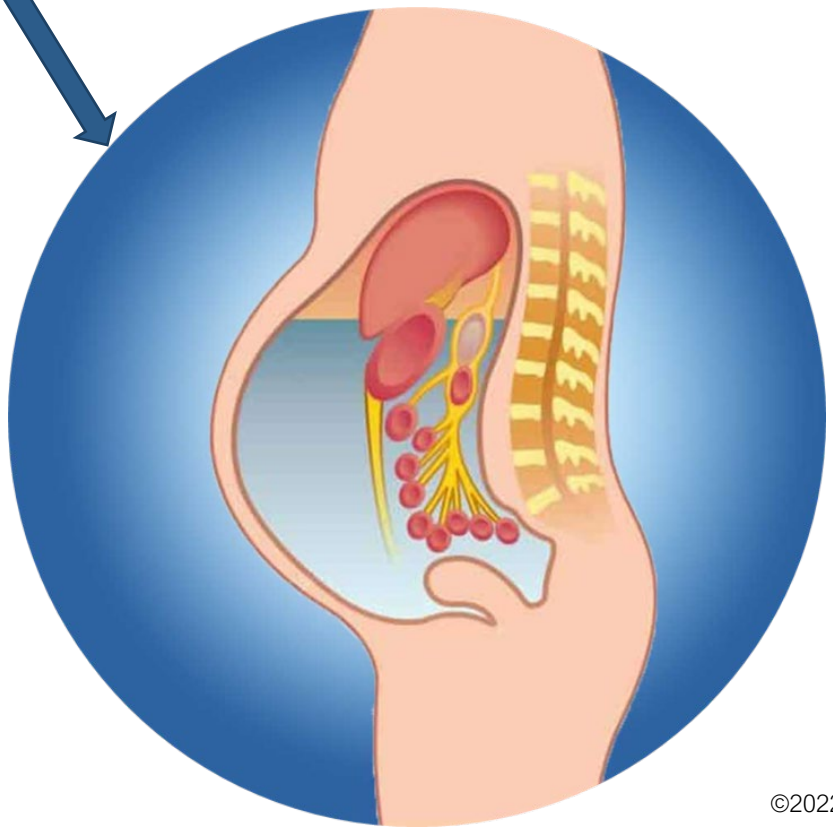
Portal hypertension

Vasodilation and blood pooling



Low arterial pressure

Activation of RAAS & SNS





# BIV201

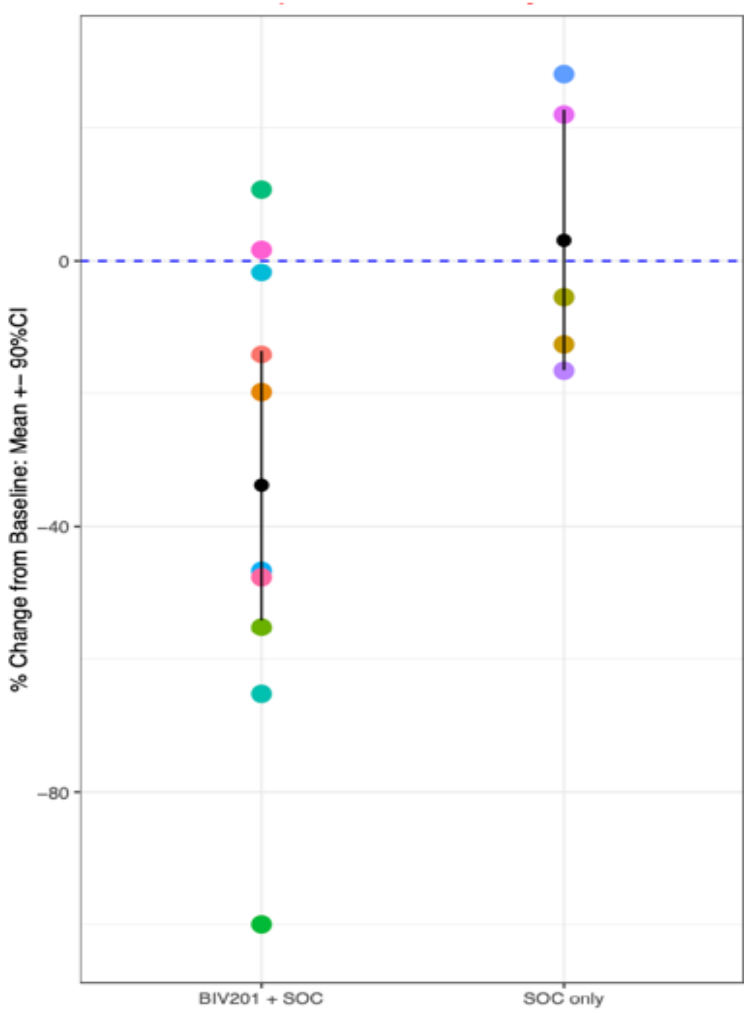
- Terlipressin administered as a continuous infusion
  - Outpatient treatment with small ambulatory infusion pump
- Targets the pathophysiology of ascites
  - Multiple small trials and Phase 2a support efficacy in reducing ascites
- Orphan and Fast Track Designations for the treatment of ascites due to all etiologies except cancer
- Mallinckrodt's Terlivaz approved in US 2022 indicated *to improve kidney function in adults with hepatorenal syndrome with rapid reduction in kidney function.* Does not impact BIV201 Clinical Program
  - Approved for different indication – Orphan market exclusivity for HRS
  - Administered in conjunction with daily albumin
  - Different dosage form and administration (intermittent bolus injections)
  - Restricted to hospital setting - black box warning
- Impacts BIV201's regulatory pathway and non-clinical package for NDA (505(b)(1))

# BIV201 Program Update

- Phase 2b - Originally targeted 30 patients randomized 2:1

- Paused enrollment based on encouraging data from the first 15 patients informing next steps
  - 10 randomized to BIV201; 5 randomized to standard of care
  - 5 completed 2 X 28-day cycles
  - 5 discontinued treatment during or at end of Cycle 1

# BIV201-treated patients experienced a 37% advantage in ascites fluid reduction compared to SOC

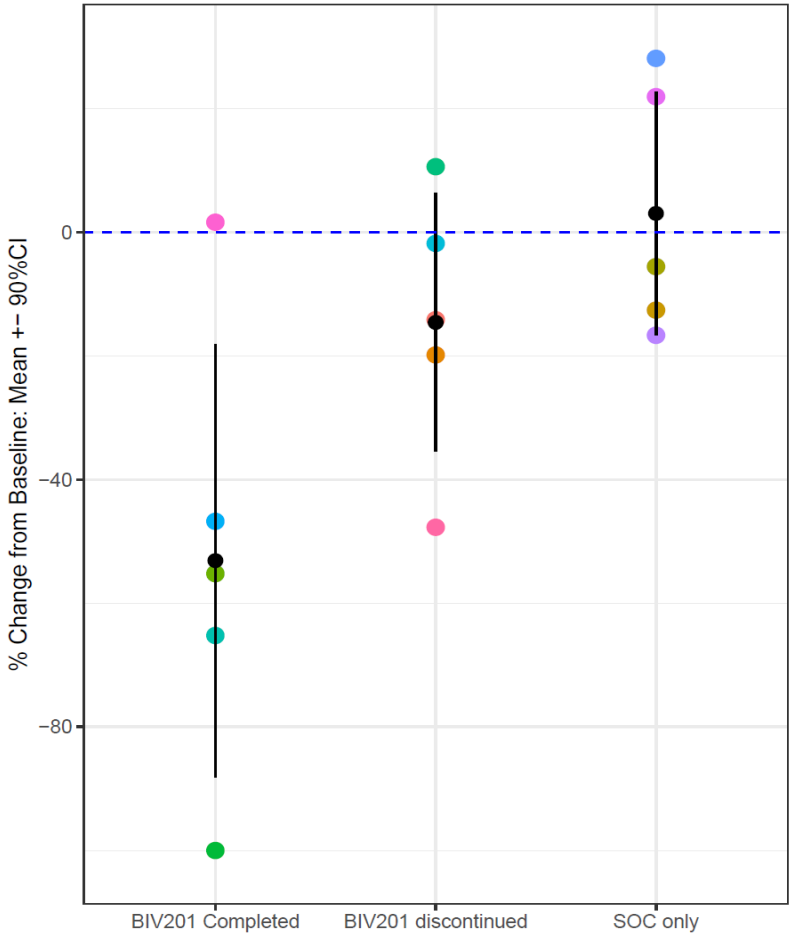



BIV201 + SOC
Mean: 34 % reduction
5/10 (50%) with >40% reduction
P=0.0046

SOC only
Mean: 3.1 % increase
0/5 (0%) with >40% reduction
P=0.8

BIV201 vs SOC
P value = 0.05 for difference

# Patients completing BIV201 treatment experienced 56% advantage in ascites fluid reduction compared to SOC




- 53% reduction in ascites volume among patient completing BIV201 treatment
- 15% reduction among patients who started but did not complete treatment
- 3.1% increase for SOC patients
- p<0.001

# Safety

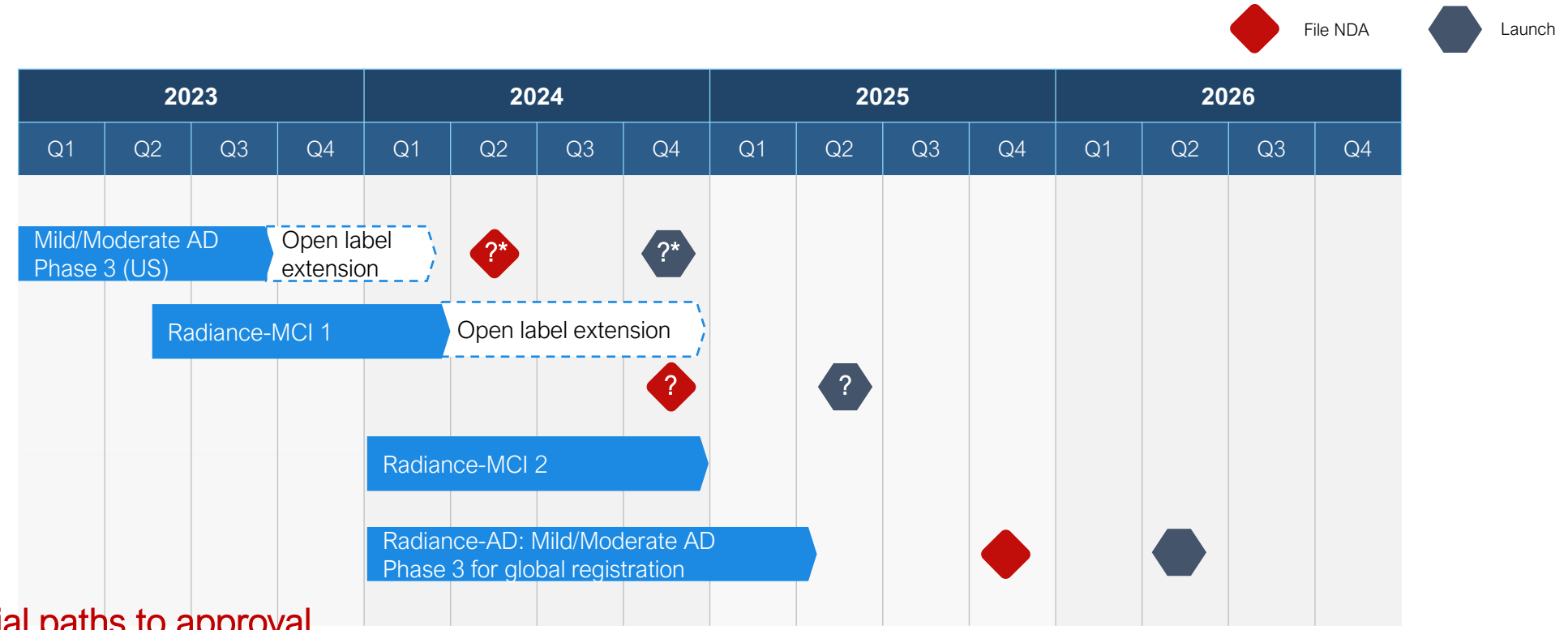
- Incidence of treatment emergent adverse events similar in both groups
- Overall safety consistent with patient population with advanced cirrhosis
- No unexpected SAEs

# Conclusions

- BIV201 treatment resulted in a reduction in ascites
- Treatment appears to be well tolerated
- Engaging FDA in discussions on next steps

# Clinical & Regulatory Strategy

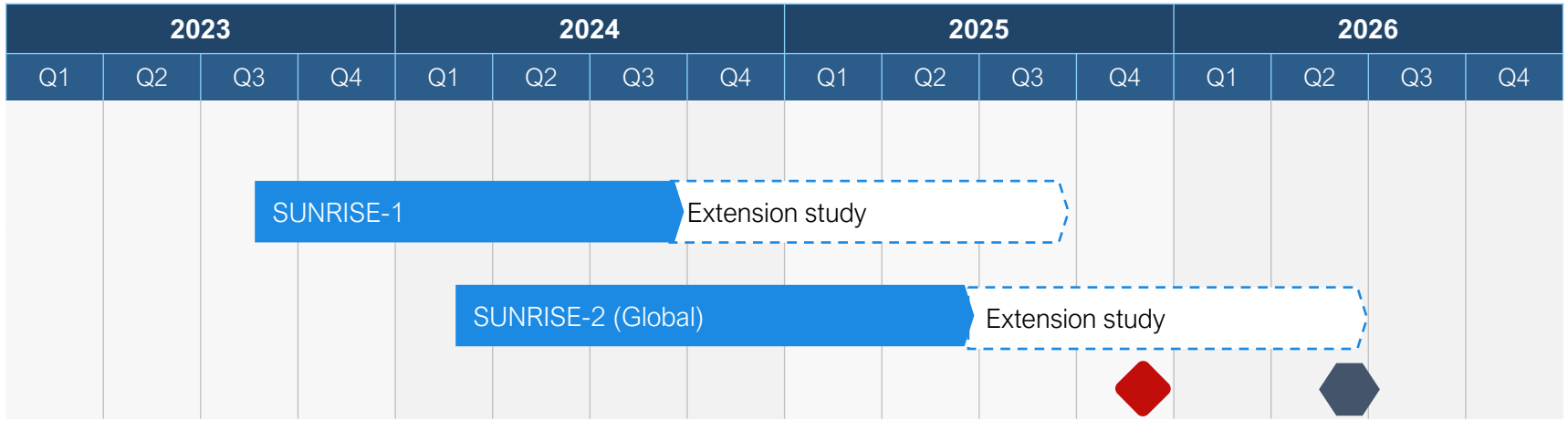
# Alzheimer's Clinical Program creates maximum optionality for approval




## Potential paths to approval

- Conditional approval based on strong clinical, functional, and objective results from single US Phase 3 pivotal in mild/moderate AD
- Regular approval for broad indication in dementia (MCI through Moderate) based on combination of positive outcomes from Phase 3 in mild/moderate and Sunrise-MCI 1
- Regular approval for mild/moderate AD from US and Global Phase 3 trials in mild/moderate

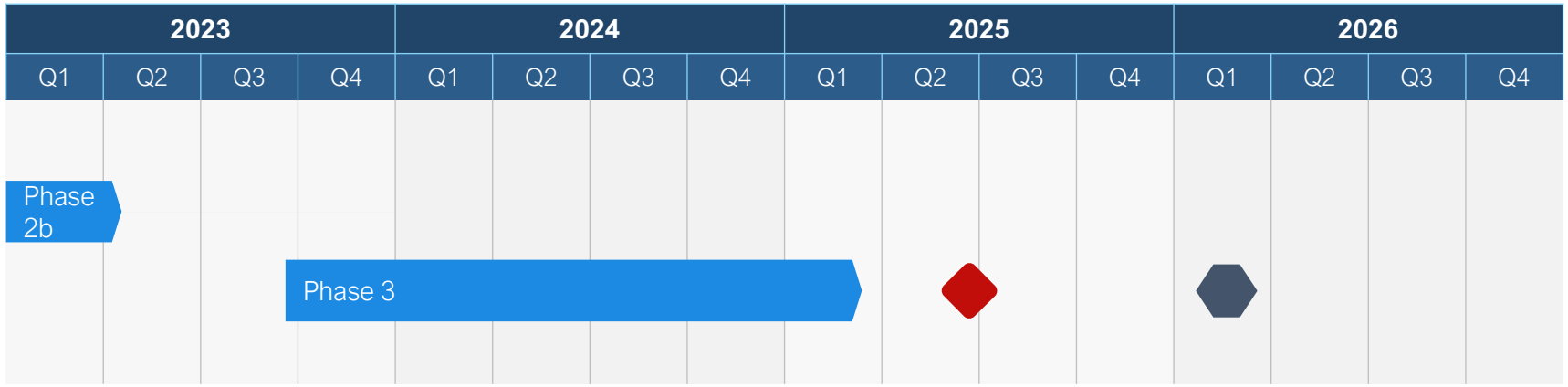
# Parkinson's clinical program is straight forward




- Both SUNRISE-1 and SUNRISE-2 are designed to serve as pivotal studies
  - Primary end-point of UPDRS Part 3 (motor) scores at 6 months
  - Extension to 18 months to demonstrate disease modification
- SUNRISE-1 adaptive design enables sample size adjustment (if needed) at 3 months
- SUNRISE-2 sample adjustment (if needed) based on SUNRISE-1 results

File NDA  Launch

# Ascites program




- Phase 2b paused with only one-half targeted patients enrolled due to statistically significant results demonstrating reduction of ascites fluid with BIV201 treatment
- Discussions initiated with FDA on path forward

File NDA  Launch

# Commercialization Roadmap

# Commercialization approach

- All options are open
- Partnering is an option
  - Initial conversation have been held
    - Some companies interested in global collaboration
    - Others in geographic rights
  - Most companies are intrigued and awaiting Phase 3 data readout
- Go-alone is always an option

# Commercial potential in US market alone

## Ascites

**$1.6B**

US peak sales

- $45K/year
- 45% market penetration
- 2026 launch
- 2032 peak sales

## Alzheimer's

**$30B**

Annual sales for every
1 million people treated

- 15% market penetration
- $30K/year – much lower all-in cost vs. competition

## Parkinson's

**$3B**

Annual sales for every
100,000 people treated

- 10% penetration of US market
- $30K/ year

Source: Company estimates

# Current finances

- $44 million cash balance as of February 28, 2023
- We have resources to fund operations through most of the year and could extend through first part of 2024 if necessary

# Social Impact

# BioVie is the founding backer of Social Impact Partners


**Mission:**

**To combat Alzheimer's and other neurodegenerative conditions and enable people to lead better and healthier lives by 1) working collaboratively, 2) raising awareness, and 3) mobilizing resources that drive innovation and new solutions.**

# SIP's Goals


1. Mobilize 1 million new healthcare workers to support individuals and families.
2. Increase public/private funding of Alzheimer's medical research 3x in 5 years and expand Medicaid/Insurance Coverage for services needed.
3. Invest and grow in 10 companies annually who advance innovative solutions.


4. Connect a global coalition of partners and individuals to promote a public and private collaboration to positively impact healthy aging and brain health.
5. Create college campus networks with Youth Ambassadors across the all countries.
6. Encourage industry collaboration (PPP's sharing preclinical models and resources).


7. Implement a significant public service ad campaign to build universal awareness of Alzheimer's.
8. Draft legislation with "Youth Board" in conjunction with consortium to present in DC & globally.
9. Support "turning passion into action" with speaker series and educational programs for universities.

# Meet our global consortium and youth board schools



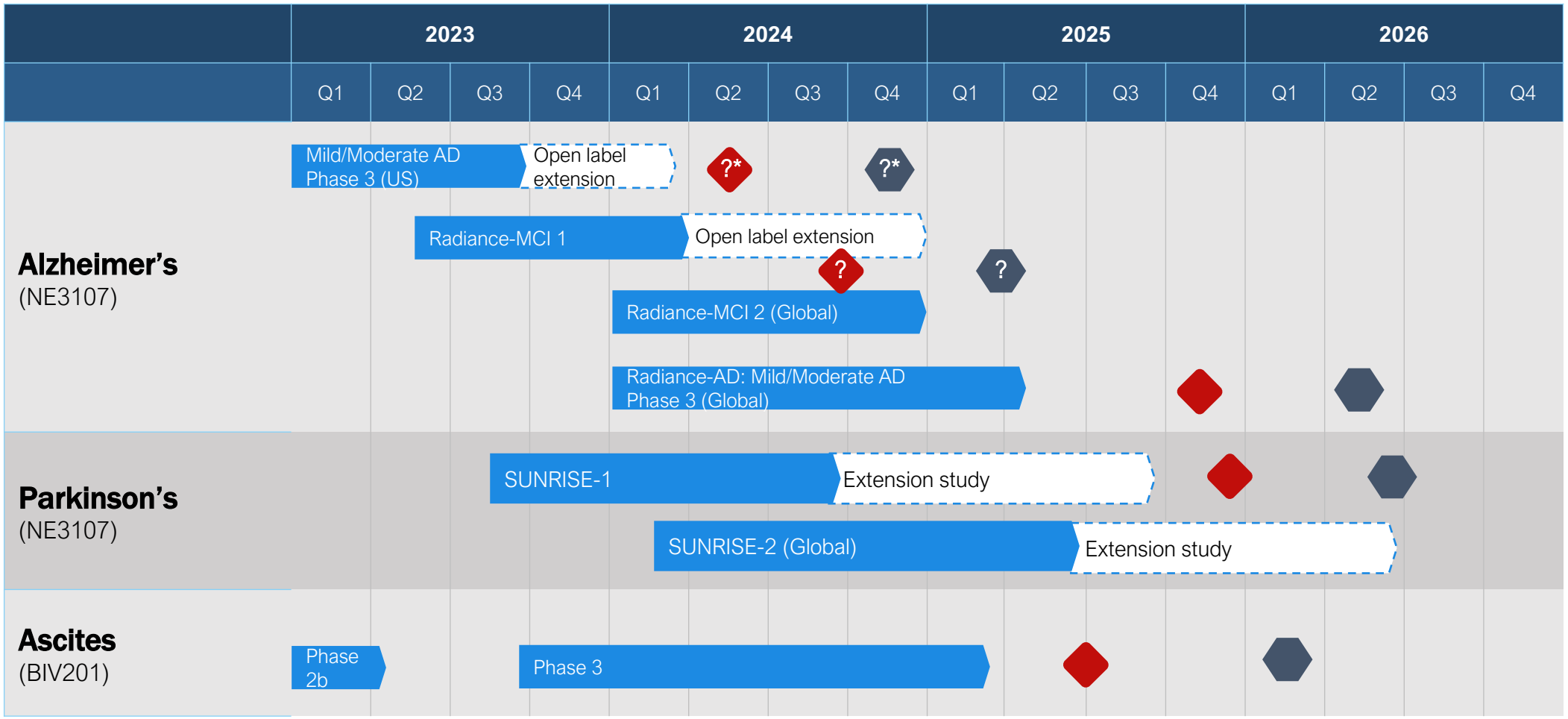

 

# Recap

# Executive Summary

- The company is in the early stages of multiple late-stage data readouts for multiple indications addressing great unmet medical needs
- Early results in Alzheimer's Disease (AD), Parkinson's Disease (PD) and Ascites have all been encouraging, and our KOLs/SAB have encouraged us to move more assertively
- Potentially pivotal registrational trials are underway or will begin in 2023 for all indications
- Topline results from our Phase 3 AD trial expected to be announced October 2023. Regulatory submissions expected in 2024 and 2025
- We believe our portfolio, if approved, will create a platform of great benefit to patients and economic value to shareholders
- All development and commercialization options (including partnering) being considered
- Our support of Social Impact Partners allows us to bring better patient-centered support to affected individuals/families, of which our future medication will be an important part

# Expected Catalysts & anticipated timelines

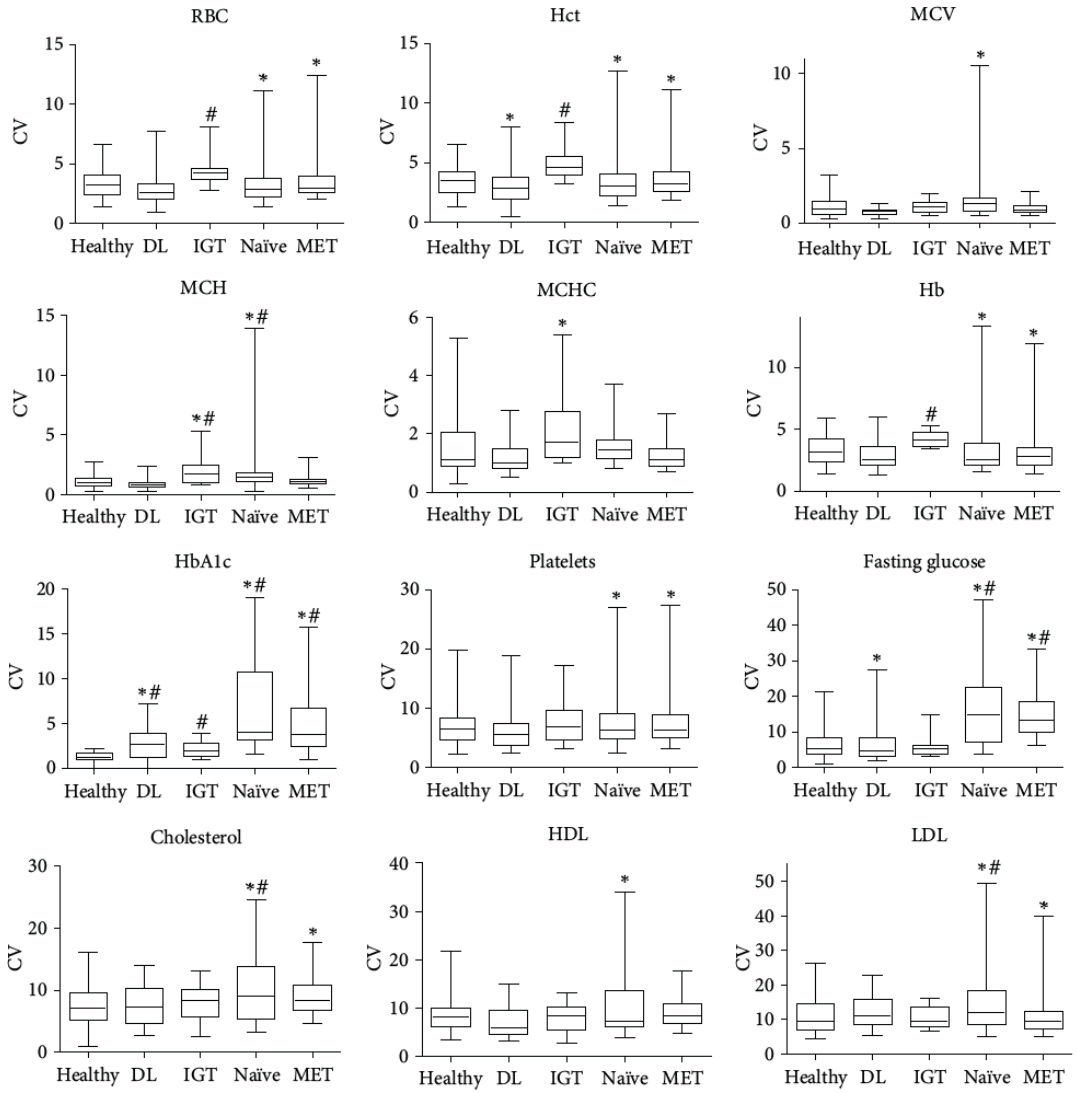



* Two Phase 3 trials are usually required for registration. However, the FDA has allowed filing based on strong data from a single pivotal trial in indications with few therapeutic options.

# Appendix

# Inflammation drives systems dysregulation

- Patients with increasing metabolic disease show greater variability for individual hematology, metabolic and chemistry values
- Indicates increasing dysregulation




DL: dyslipidemic placebo group, IGT: impaired glucose tolerant placebo group, Naïve: treatment-naïve uncontrolled T2DM placebo group, MET: uncontrolled T2DM placebo group on a stable dose of metformin

RBC: red blood cell count, Hct: hematocrit, MCV: mean cell volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, Hb: hemoglobin, HbA1c: hemoglobin A1c, HDL: high density lipoprotein cholesterol, LDL: low density lipoprotein cholesterol.

# Statistically Significant Welch ANOVA).

∗ Statistically significant 2-sided $FF$ test.

Reading 2013 *Mediators Inflamm 814989*



# NE3107 decreased systems dysregulation in a Phase 2 study

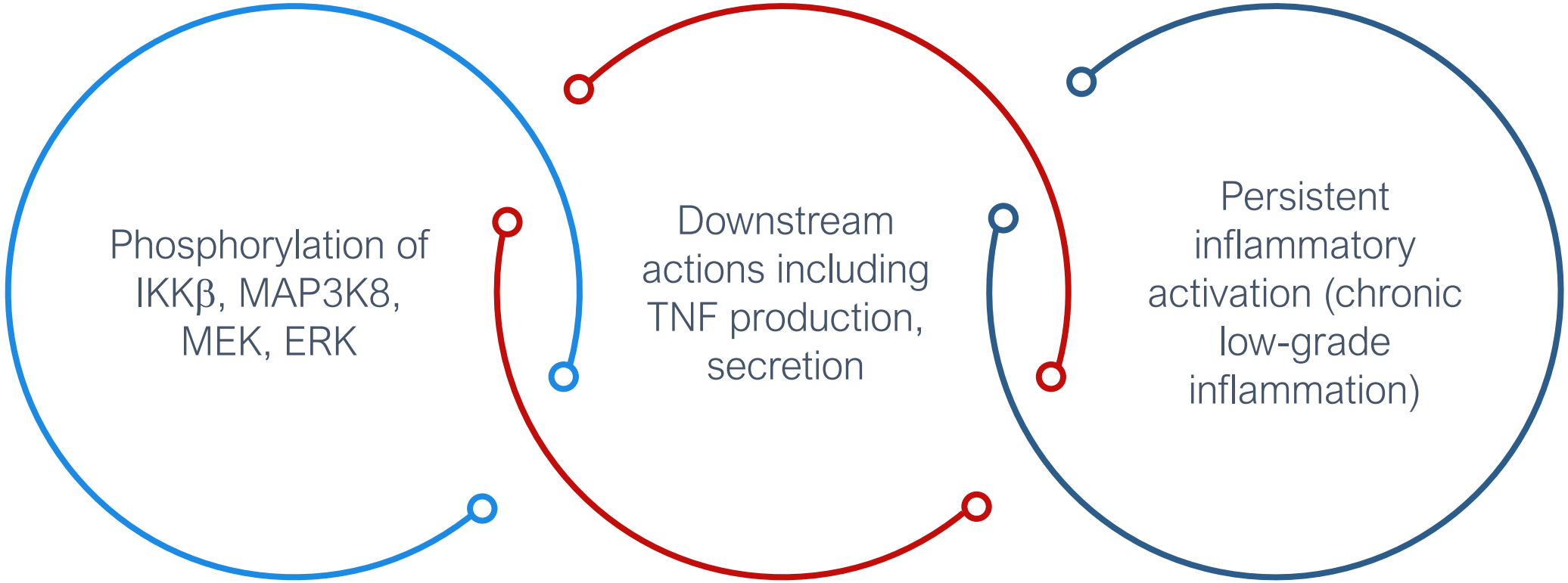
- Heteroscedasticity* investigated by analyzing data distributions for normality (Shapiro-Wilks $W$ test)
  - Deviations from normal distribution represents dysregulation
- Placebo patients had significantly abnormal data distributions after 84 days of treatment whereas NE3107 subjects did not
  - Placebo patients had many parameters that significantly deviated from normal distribution (i.e., dysregulated)
  - NE3107 treatment reduced systems dysregulation

| Group | Day | Parameter | HE3286 *W* test *P* | Placebo *W* test *P* |
|---|---|---|---|---|
| Cohort 1 | 84 | ΔInsulin[d] | >0.1 | **<0.0001** |
| | | ΔC-peptide | >0.1 | **<0.0001** |
| | | ΔFasting glucose | >0.1 | **0.02** |
| | | ΔHOMA2 %B | >0.1 | **<0.0001** |
| | | ΔHOMA2 IR | >0.1 | **0.002** |
| | | Δleptin | >0.1 | **0.005** |
| Cohort 1 MCP-1 > 40[b] | 84 | ΔHbA1c | >0.1 | **0.006** |
| | | ΔFasting glucose | >0.1 | **0.02** |
| | | ΔHOMA2 %B | >0.1 | **<0.0001** |
| Cohort 2 | 84 | ΔnHbA1c | >0.1 | **0.04** |
| | | ΔInsulin | >0.1 | >0.1 |
| | | ΔFasting glucose | >0.1 | **0.03** |
| | | ΔHOMA2 %B | >0.1 | >0.1 |
| | | ΔMCP-1 | >0.1 | **0.005** |
| | | ΔTriglycerides | >0.1 | **<0.0001** |
| | 112 | ΔnHbA1c | >0.1 | **0.0007** |
| | | ΔInsulin | >0.1 | >0.1 |
| | | ΔFructosamine | >0.1 | **0.002** |
| | | ΔHOMA2 %B | >0.1 | **<0.0001** |
| Cohort 2 BMI > 31[c] | 84 | ΔHOMA2 %B | >0.1 | **0.007** |
| | | ΔMCP-1 | >0.1 | >0.1 |
| | | ΔTriglycerides | >0.1 | >0.1 |
| | 112 | ΔInsulin | >0.1 | **<0.0001** |
| | | ΔC-peptide | >0.1 | **<0.0001** |
| | | ΔHOMA2 %B | >0.1 | **<0.0001** |
| | | ΔHOMA2 IR | >0.1 | **<0.0001** |

* Heteroscedasticity describes differences in variances between groups.
Reading 2013 *Mediators Inflamm 814989*
Note: NE3107 was originally known as HE3286 from Hollis Eden Pharmaceuticals

# NE3107's inhibition of inflammatory signaling

NE3107 binds to ERK in the NFκB scaffold complex, and alters the scaffold conformation, inhibiting



# Homeostatic insulin signaling

01

Hyperglycemia increases insulin, which binds to the insulin receptor (IR) on cells in muscle, liver, adipose tissue, brain, pancreas, etc.

02

Insulin binding to IR triggers IR phosphorylation of insulin receptor substrate 1 & 2 (IRS1/2) on tyrosine, activating Phospho-inositol 3 kinase (PI3K) and MAPKs RAF, MEK and ERK

03

PI3K feeds back to phosphorylate IRS1/2 on serine, inhibiting further stimulation as glucose is taken up in cells in response to insulin



# Inflammatory inhibition of Insulin signaling

As in macrophage lineage cells, the NFkB resting scaffold is present in these insulin target cells

Inflammatory mediators (e.g., Amyloid β, alpha-synuclein, TNF, fatty acids) activate NFκB, IKKβ, as in macrophages

IKKβ is a serine kinase, and phosphorylates serine on IR, blocking PI3K and ERK homeostatic signaling and resulting in insulin resistance

# NE3107 restoration of Insulin sensitivity