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Sage Therapeutics *FutureCast*

An R&D and Portfolio Review

Safe Harbor Statement

- The slides presented today and the accompanying oral presentations contain forward-looking statements, which may be identified by the use of words such as “may,” “might,” “will,” “should,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “opportunity”, “goal”, “potential,” or “continue,” and other similar expressions. Forward-looking statements in this presentation include statements regarding: our clinical development plans and expected timelines; the potential regulatory pathways for our product candidates; our belief in the potential of our product candidates in various indications; the potential profile and benefit of our product candidates; our estimates as to the number of patients with disorders and diseases of interest to us; the goals, opportunity and potential for our business; and our views with respect to potential value creation opportunities and our ability to become a multi-franchise, leading brain health company. These forward-looking statements are neither promises nor guarantees of future performance, and are subject to a variety of risks and uncertainties, many of which are beyond our control, which could cause actual results to differ materially from those contemplated in these forward-looking statements, including the risk that:
- we may not be successful in our development of any of our product candidates in any indication we are currently pursuing or may in the future pursue; success in earlier non-clinical studies or clinical trials of our product candidates may not be repeated or observed in ongoing or future studies involving the same compound or other compounds, and non-clinical and clinical results for our product candidates may not support further development of the product candidate or regulatory approval on the timelines we expect or at all or may require additional clinical trials or nonclinical studies. Even if our planned development programs are successful, we still may not achieve review or approval, despite prior regulatory advice, and regulatory authorities may ask for additional trials or data.
- we may not be able to mitigate the impact of COVID-19 on our clinical development timelines and the impact may be more significant than we expect and may negatively impact expected site initiation, enrollment or conduct in our clinical trials, or cause us to pause trials or not be able to use data, in each case which may significantly impact our ability to meet our expected time-lines or may significantly impact the integrity or sufficiency of the data from our trials or increase our costs or cause us to have to change our plans; we may experience slower than expected enrollment in our clinical trials for other reasons or may encounter other delays or problems, including in analyzing data or requiring the need for additional analysis, data or patients, and such issues with any trial could cause delay in completion of the trial, availability of results and timing of future activities.
- we may encounter unexpected safety or tolerability issues with respect to any of our product candidates or marketed products; we may encounter different or more severe adverse events at the higher doses or in new indications we are studying in new trials; we may encounter issues with the efficacy or durability of short-term treatment, or co-initiated treatment with zuranolone or safety and efficacy concerns with respect to retreatment that require additional studies be conducted;
- the FDA may ultimately decide that the design or results of our completed and planned clinical trials for any of our product candidates, even if positive, are not sufficient to file for or obtain regulatory approval in the indications that are the focus of our development plans; other decisions or actions of the FDA or other regulatory agencies may affect the initiation, timing, design, size, progress and cost of clinical trials and our ability to proceed with further development; we may encounter technical and other unexpected hurdles in the development and manufacture of our product candidates which may delay our timing or change our plans or increase our costs;
- the internal and external costs required for our ongoing and planned activities, and the resulting impact on expense and use of cash, may be higher than expected which may cause us to use cash more quickly than we expect or change or curtail some of our plans or both;
- Even if our products are successfully developed and approved, the number of patients with the diseases or disorders our products treat, and the actual market for such products may be smaller than our current estimates; or we may not achieve market acceptance or reimbursement at acceptable levels;
- We may face competition from others developing products for similar uses as those for which our products are being developed; and
- We may not be able to obtain and maintain adequate intellectual property protection or other forms of data and marketing exclusivity for its products, or to defend ours patent portfolio against challenges from third parties; we may face competition from others developing products for similar uses as those for which our products are being developed.

For additional disclosure regarding these and other risks Sage faces, see the disclosure contained in the "Risk Factors" section of our most recent quarterly report, and in our other public filings with the Securities and Exchange Commission, available on the SEC's website at http://www.sec.gov. Any forward-looking statement represent our views only as of today, and should not be relied upon as representing our views as of any subsequent date. We undertake no obligation to update or revise the information contained in this presentation, whether as a result of new information, future events or circumstances or otherwise.

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Presenters

- **Jim Doherty, Ph.D.**
  Chief Research Officer
- **Mike Quirk, Ph.D.**
  Vice President, Pharmacology

  Aaron Koenig, M.D.
  M.D., Senior Medical Director, Early Development
- **Helen Colquhoun, M.D.**
  M.D., Vice President, Early Development
- **Rob Lasser, M.D.**
  Vice President, Late Development
- **Greg Mattingly, M.D.**
  Associate Clinical Professor at Washington University
- **Steve Kanes, M.D.**
  Chief Medical Officer
- **Jeff Jonas, M.D.**
  Chief Executive Officer

Agenda

Sage's approach to exploratory clinical research and the questions we ask

Sage's NMDA Discovery Efforts: An emerging platform of NMDAr modulators

SAGE-324: Novel potential treatment for chronic neurological conditions

Zuranolone: Exploring the fundamentals of an 'as needed' treatment in MDD

Brexanolone and COVID-19 related ARDS

Conclusion / Q&A

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Sage's Approach to Exploratory Clinical Research and Drug Development

The questions we ask…

Jim Doherty, Ph.D.
Chief Research Officer

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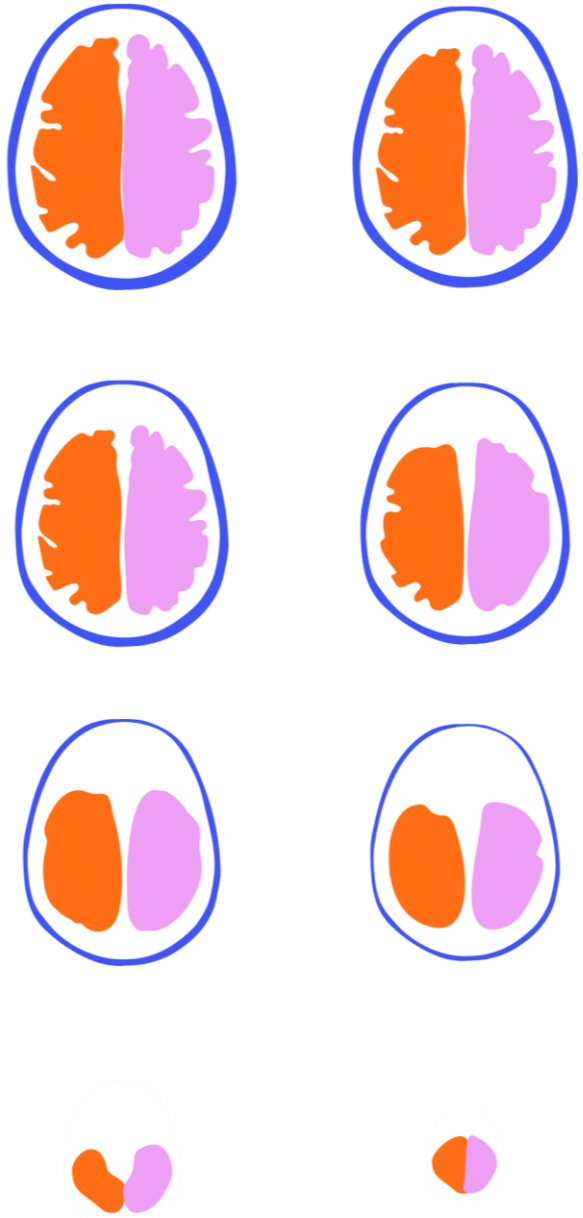
Sage's R&D Strategy

- Focus on understanding how modifying key brain receptors – $GABA_A$ and NMDA receptors – impacts brain function at the network level to guide:
  - Preclinical studies that model the potential impact of our molecules on network function in experimental systems
  - Emphasis on translatable endpoints in clinical development that can be used to understand how our candidate drugs may influence the human brain
- The questions we ask in our discovery and development programs are designed to be proactive and predictive:
  - Proactively follow the science with discovery efforts
  - Lead with human data to predictively approach drug development



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Sage's NMDA Discovery Efforts: *An emerging platform of NMDAr modulators*

Mike Quirk, Ph.D.
Vice President, Pharmacology

Aaron Koenig, M.D.
Senior Medical Director,
Early Development

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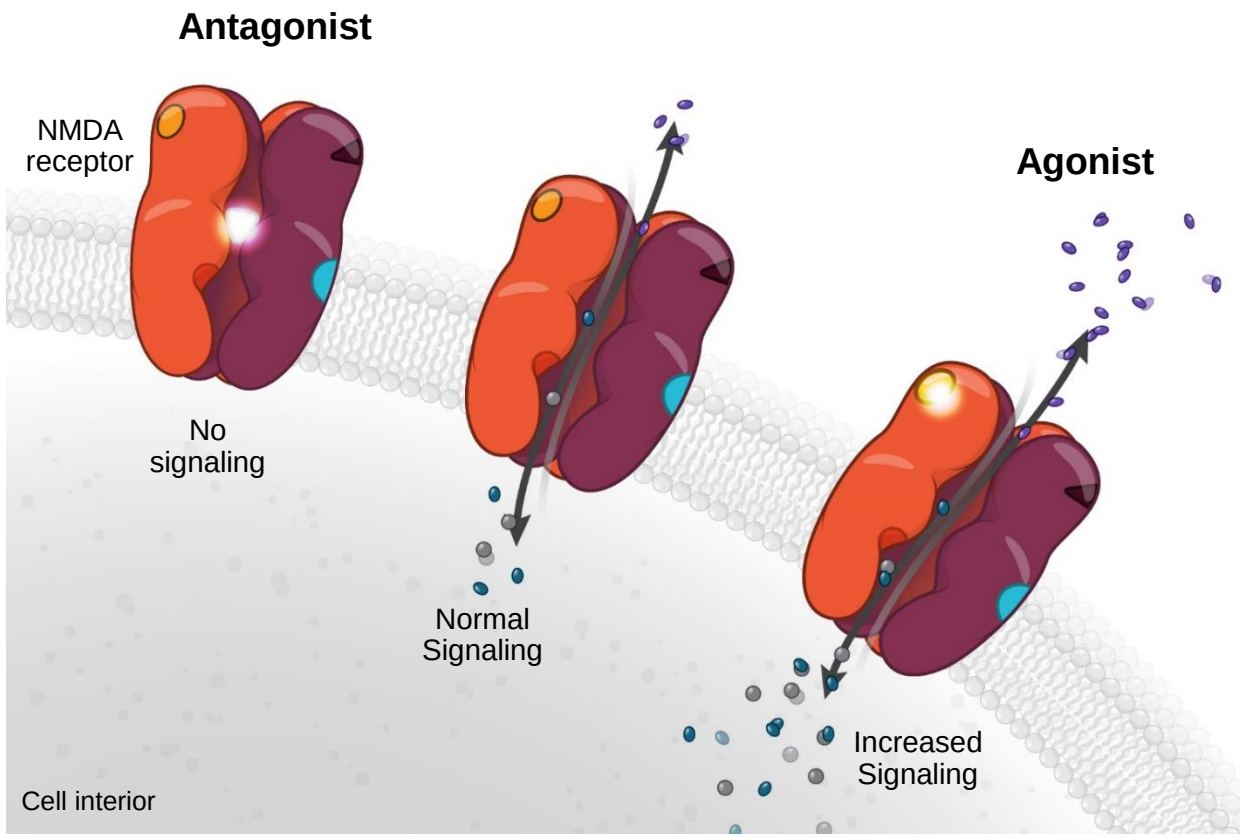
NMDA Receptors: Opportunity and Challenges

- Key components of excitatory neurotransmission
- Play critical role in brain plasticity, neuronal network stabilization and brain health
- Decades of research has postulated that NMDA receptors are essential for cognition and behavior
- Challenge: Effectively target NMDA receptors while achieving an appropriate benefit:risk profile

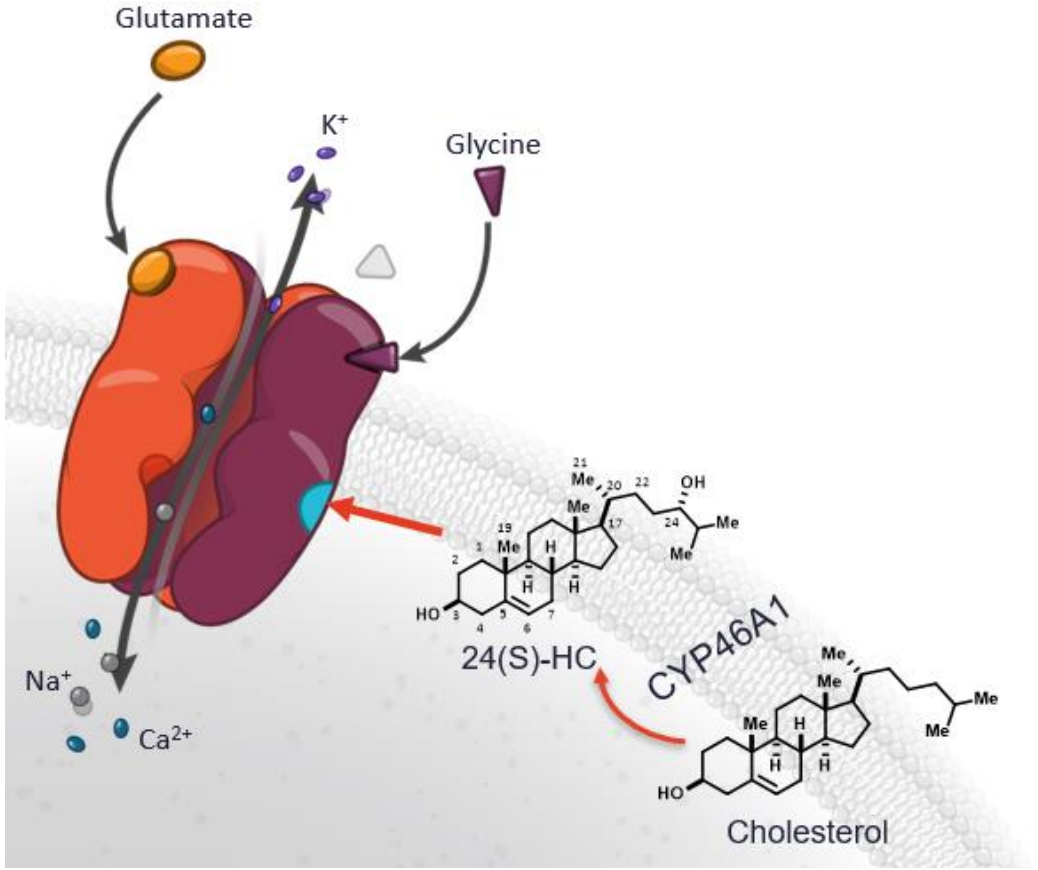


First-in-Class NMDA Receptor PAMs

Novel Starting Point for Understanding NMDA Receptor Modulation

Emerging science drives new thinking

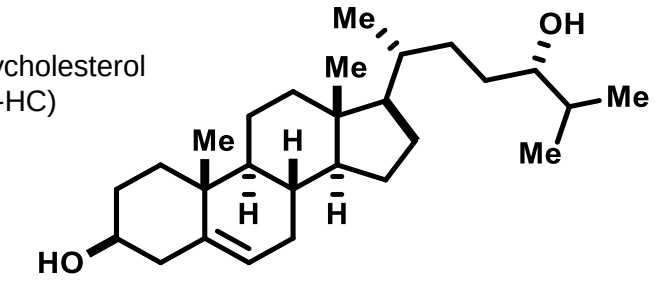
- 24S-hydroxycholesterol (24S-HC) is a cholesterol metabolite produced primarily in the brain
- 24S-HC positively modulates NMDA receptors (PAM)
- Plasma 24S-HC is a potential biomarker for patient populations or diseases with NMDAr dysfunction



Sage Has Developed a Robust Library of NMDAr Modulators

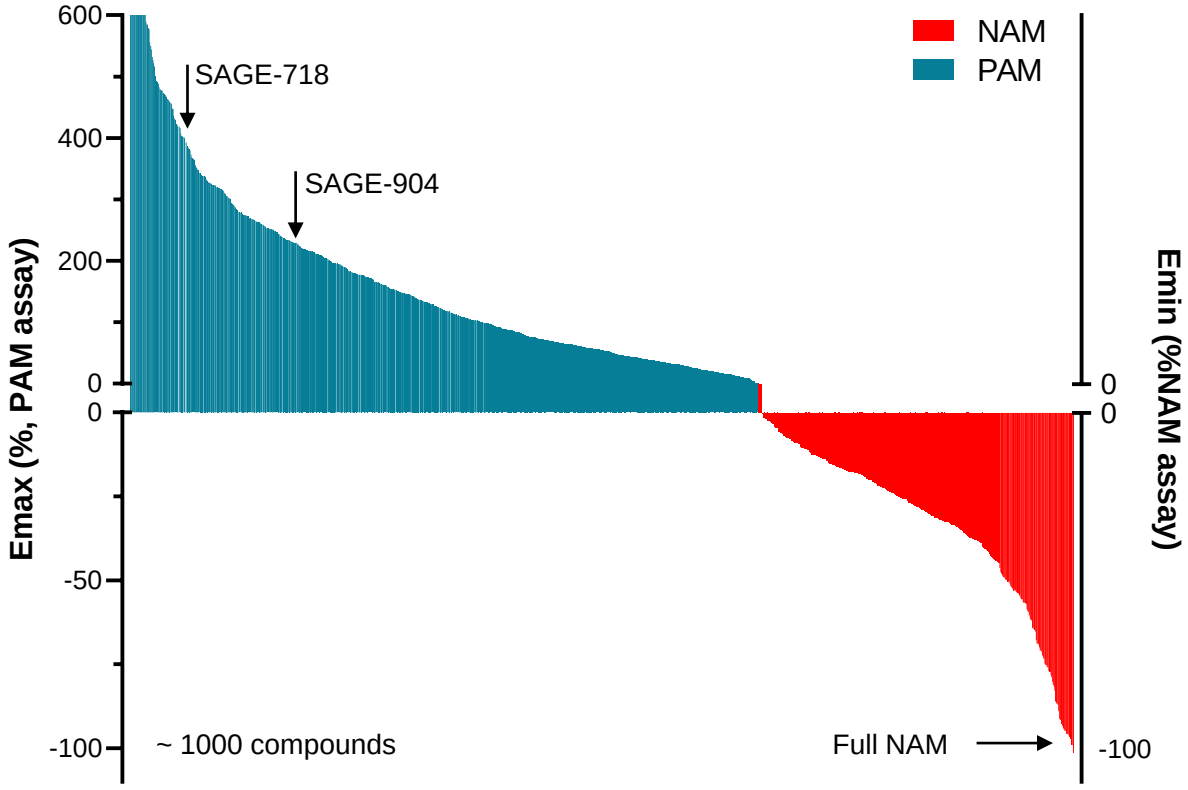
Creating a portfolio of drug-like molecules targeting NMDA receptors

24S-hydroxycholesterol
(24S-HC)



		24S-HC Endogenous	SGE-301 Research Tool	SAGE-718 Clinical	SAGE-904 Clinical
Pharmacology	EC50	220 nM	480 nM	<100 nM	~100 nM
	Emax	160%	220%	> 400%	< 400%
Drug-like Properties		Poor	Poor	Good	Good

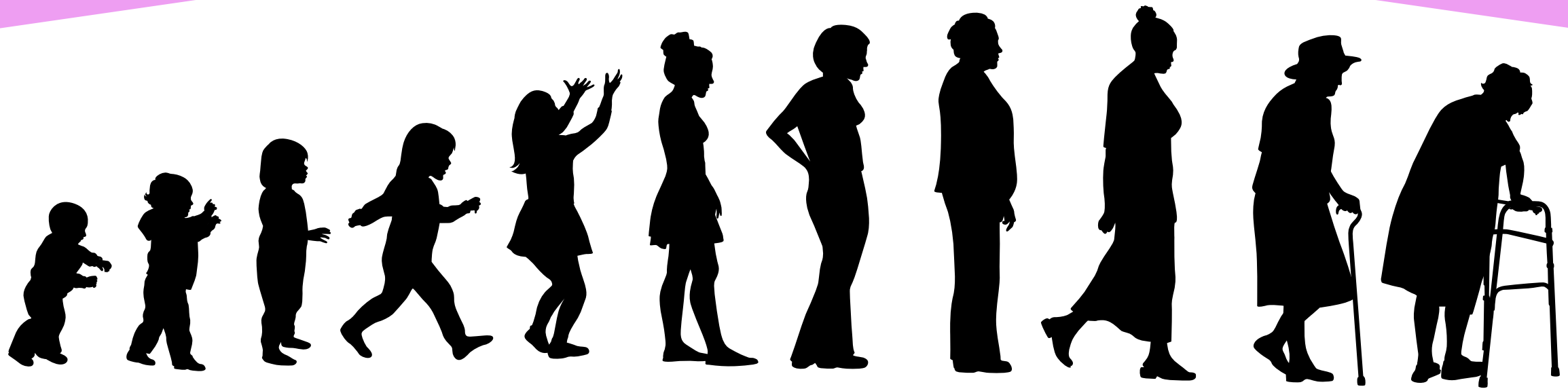
Robust library of novel oxysterol-based NMDA modulators, with unique profiles



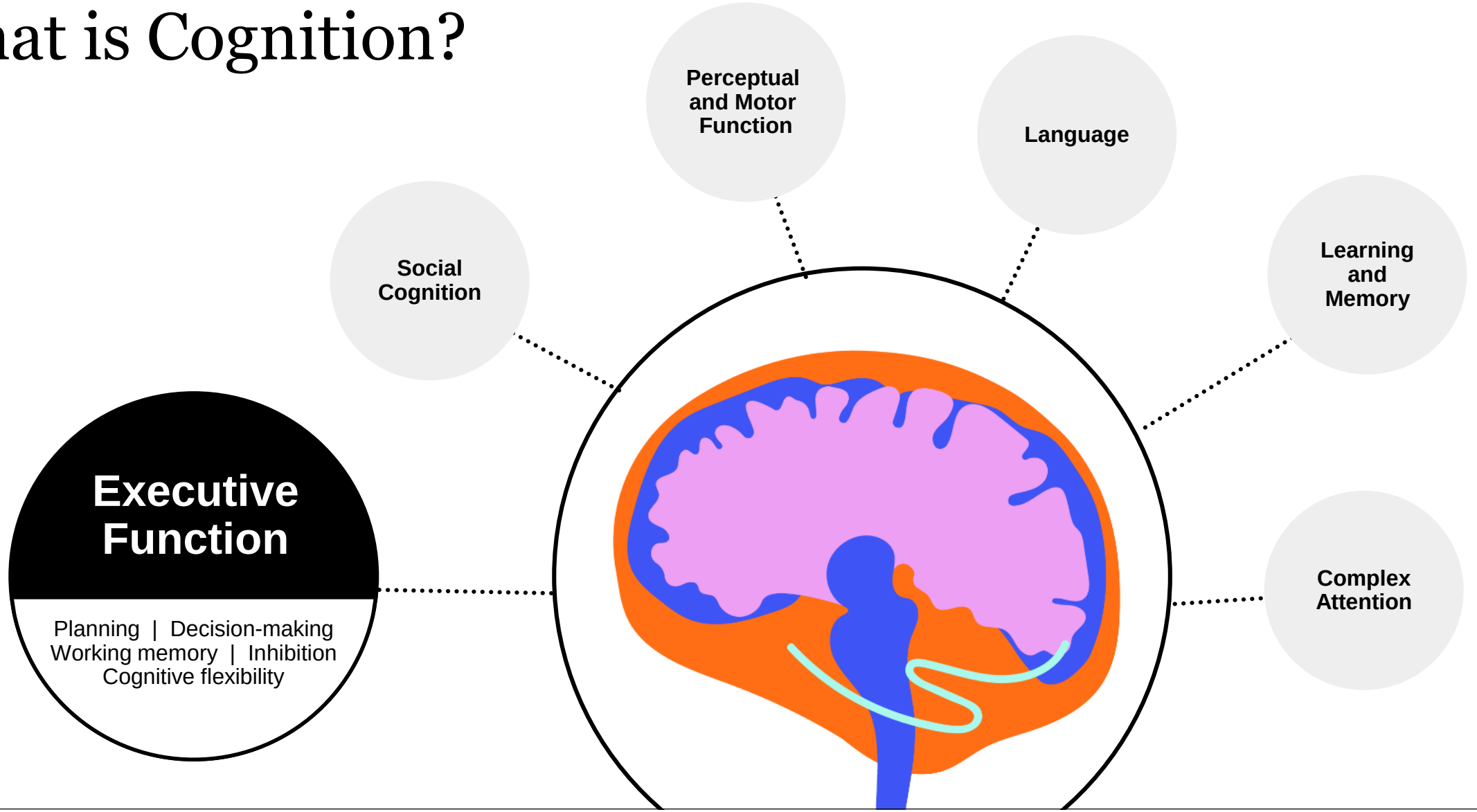
Sage Neuropsychiatry: Addressing Disorders of Cognition & Behavior Across the Lifespan

Cognitive Rehabilitation

Neurodevelopmental **Neurodegenerative**



What is Cognition?



Sachdev, P et al. (2014). Classifying neurocognitive disorders: The DSM-5 approach. Nature Reviews

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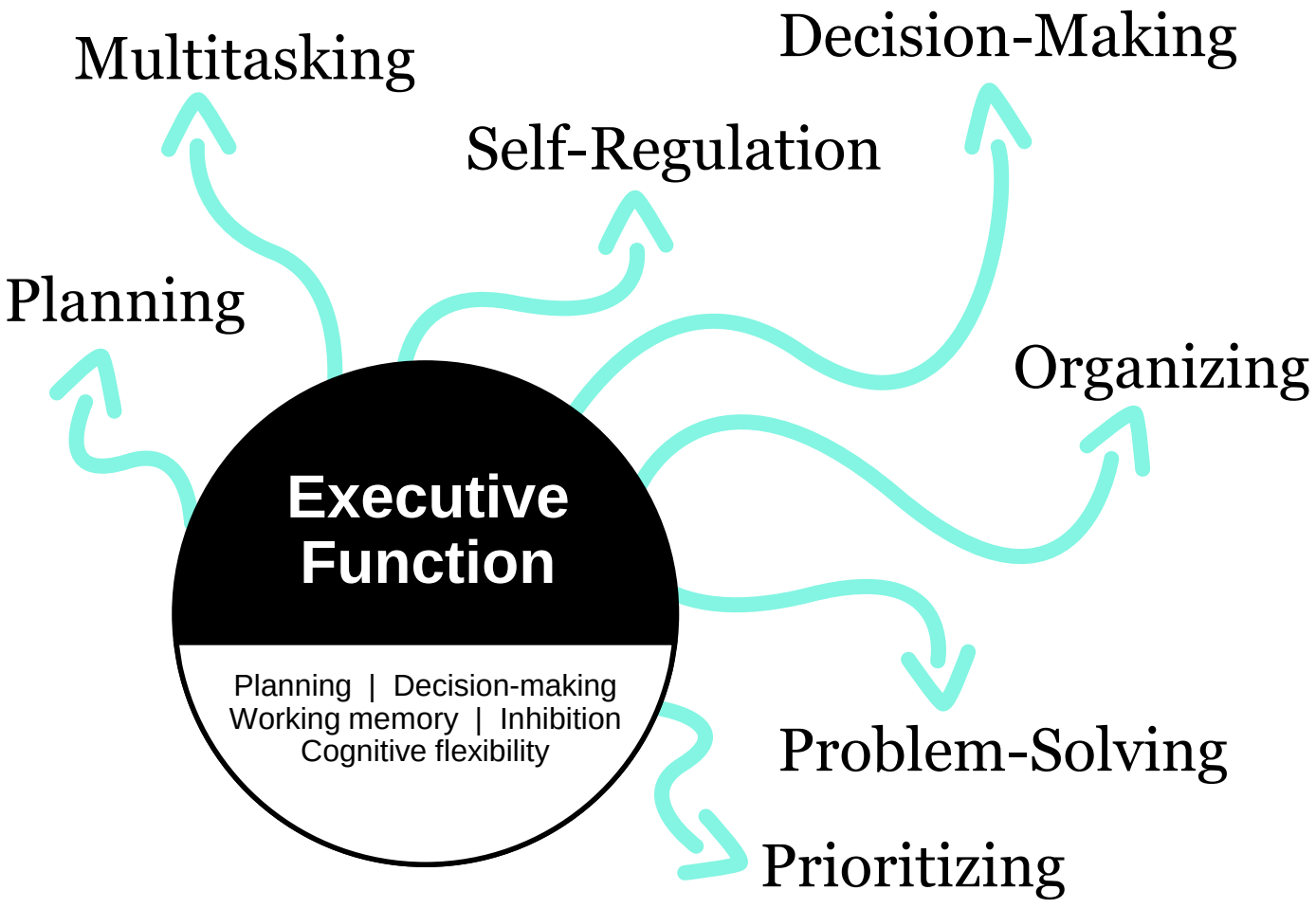
Executive Functioning



Primary cognitive deficit in:

- Frontotemporal Dementia
- Huntington's Disease
- Parkinson's Disease

Secondary but important deficit in:

- ADHD
- Alzheimer's Disease
- Autism Spectrum Disorders

Qualitative Interviews* with Patients Reveal the Real-World Implications of Executive Deficits (and Unmet Medical Need)

I've been at my office for four and a half years, and **I'm starting to make mistakes that I've never made**…

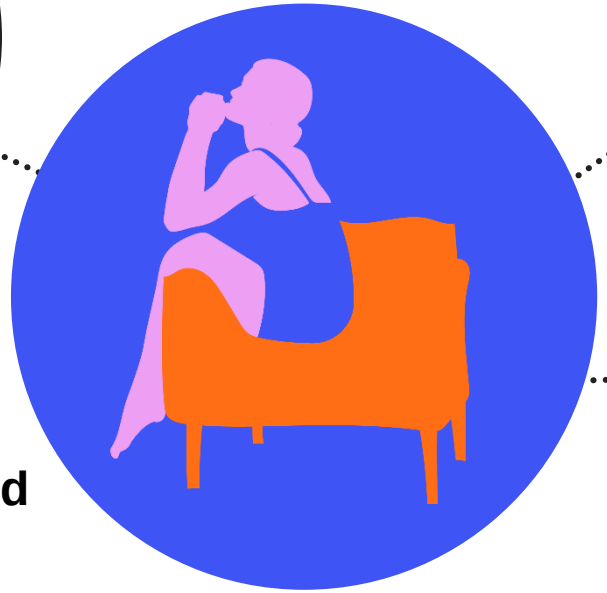
Interfering with work

I was **never the best at managing finances** to begin with**, but it's been even harder**. **Now, I've completely handed it over to my husband…**

Trouble managing finances

If something changes, I tend to be a little bit of a mess. My husband has to kind of help me work through it.

Difficulty coping with change



40 year old female

*Sage conducted semi-structured interviews with patients (n=25) and care partners (n=10) to identify the functional impact of HD cognitive impairment in early HD. Interviews explored cognitive symptom experience and functional impact. Note: Patient responses have been edited for clarity

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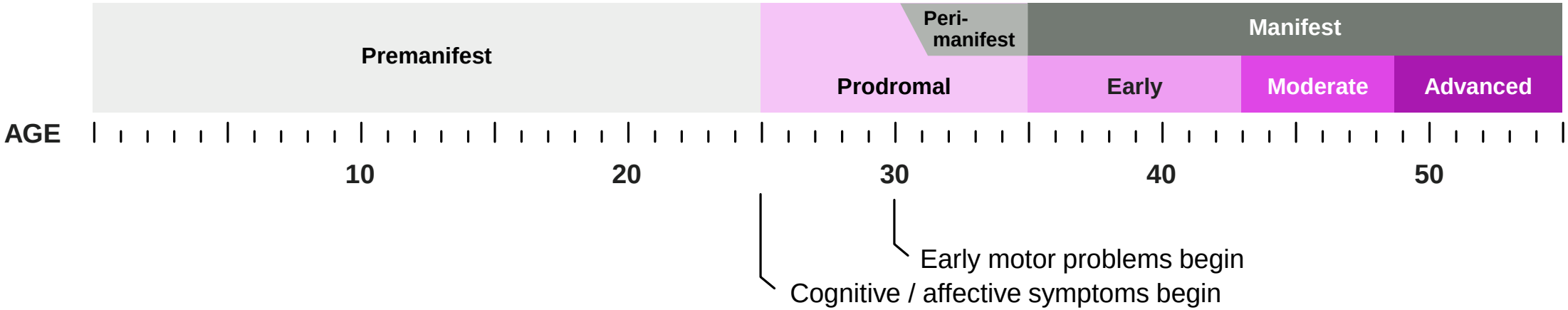
Example: Huntington's Disease

- A neurodegenerative disorder characterized by choreiform movements, psychiatric problems, and cognitive changes
- Caused by a cytosine-adenine-guanine (CAG) trinucleotide repeat expansion in the huntingtin gene, inherited in an autosomal-dominant pattern
- Course is one of slow but relentless deterioration

Representation of the lifespan of an HD expansion carrier



Bates, Tabrizi and Jones. "Huntington's Disease." Oxford University Press, 2014

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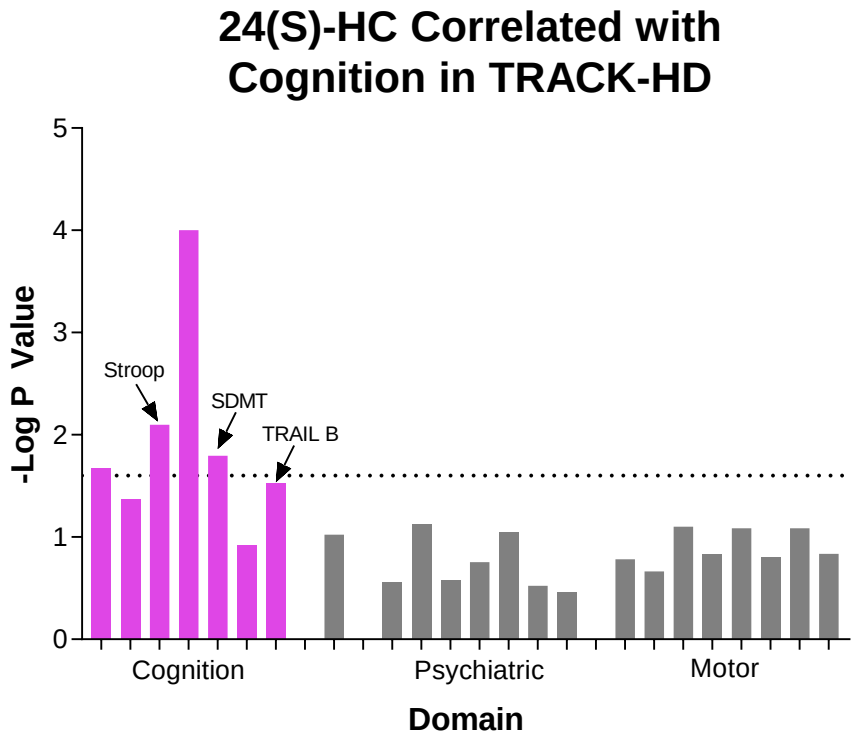
SAGE Translational Science:

Plasma 24(S)-HC levels correlated with cognitive impairment in early HD

- Exploratory analysis of the relationship between 24(S) and all of the endpoints collected as part of TRACK-HD
- 24(S)-HC was not associated with performance on motor tasks
- Plasma levels of other oxysterols (25-HC and 27-HC) did not show significant associations with cognition in HD

Therapeutic hypothesis: *NMDA modulators, acting similarly to 24(S)-OHC, may help to restore NMDA activity and alleviate aspects of this cognitive dysfunction in patients with early Huntington's Disease*



HSG 2019 abstract Lewis et al "Cognitive Deficits in Huntington's Disease and Altered 24(S) Hydroxycholesterol"

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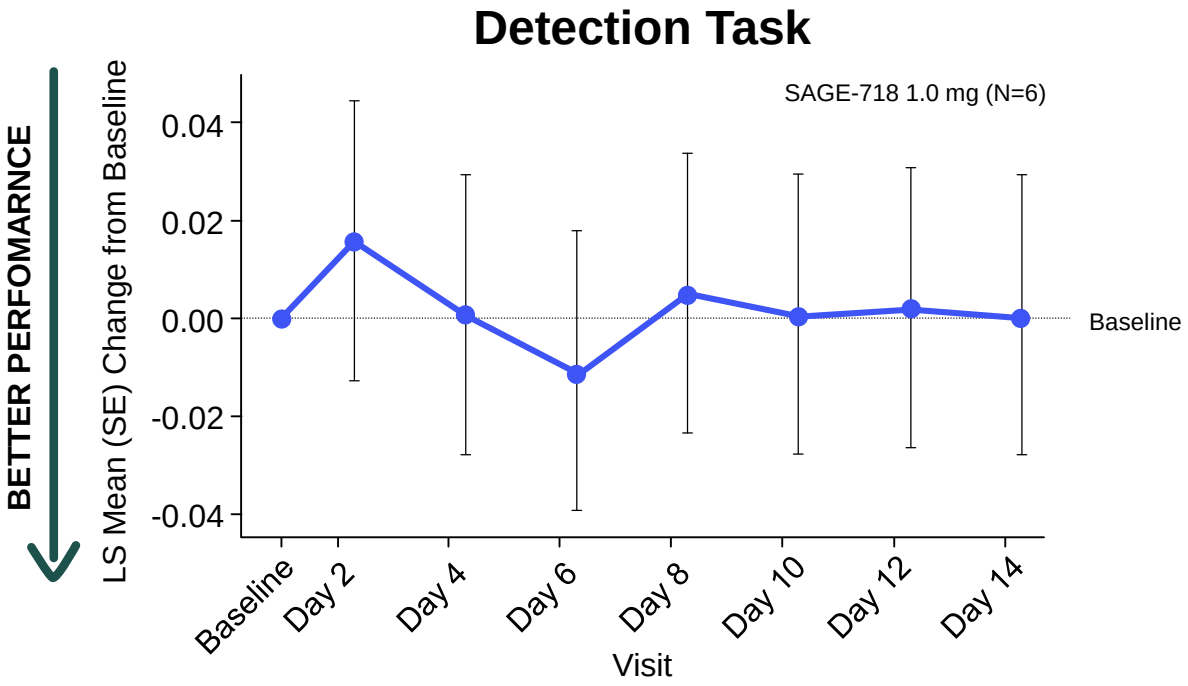
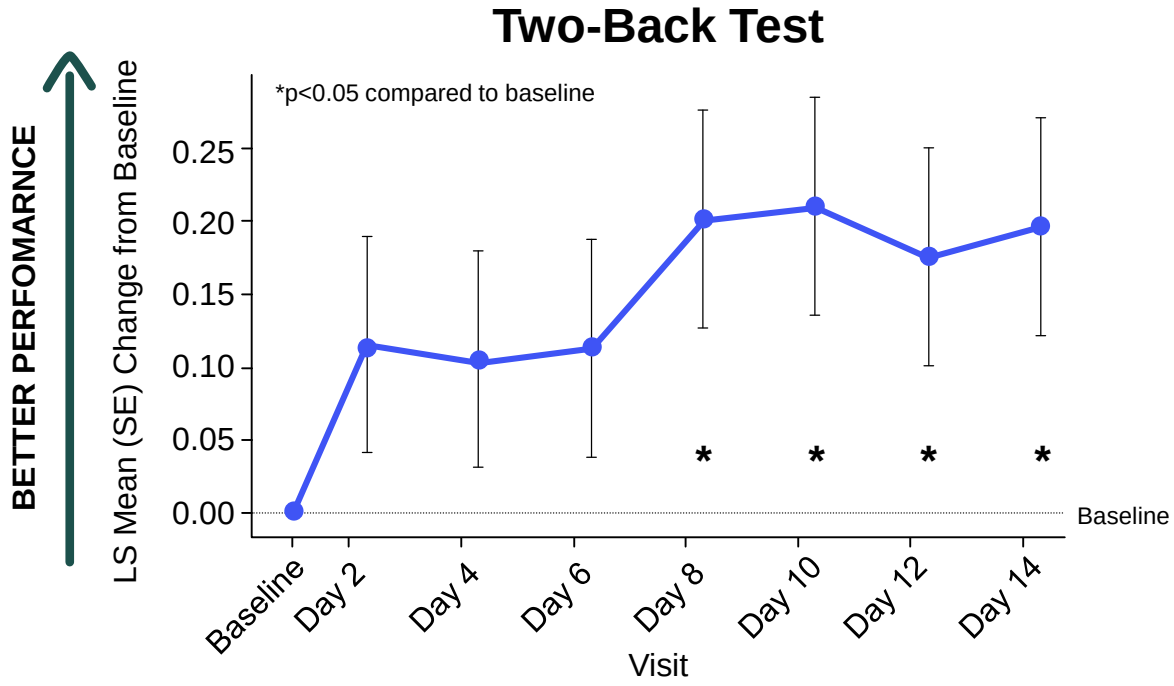
Cognitive Performance in Patients w/ Early HD Treated with Open-Label Sage-718 Over 2 Weeks





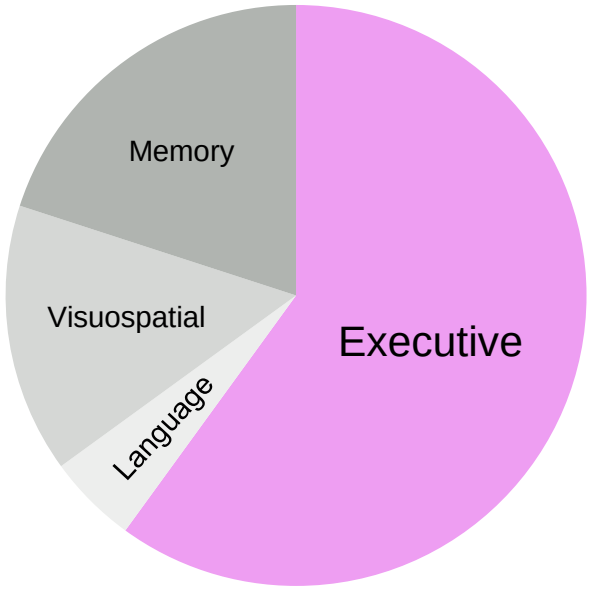
VARIABLE	MEAN (SD)	RANGE
Total Functional Capacity	11.3 (2.87)	(7, 13)
Baseline MoCA	23.3 (4.99)	(16, 27)
UHDRS Motor Score	7.5 (5.26)	(0,12)

Subjects had mild to moderate disease (HD1 or HD2, defined by TFC) and cognitive impairment at baseline

In Phase 1 studies of SAGE-718 no serious adverse events or deaths have occurred, and most treatment-emergent adverse events have been mild in severity.

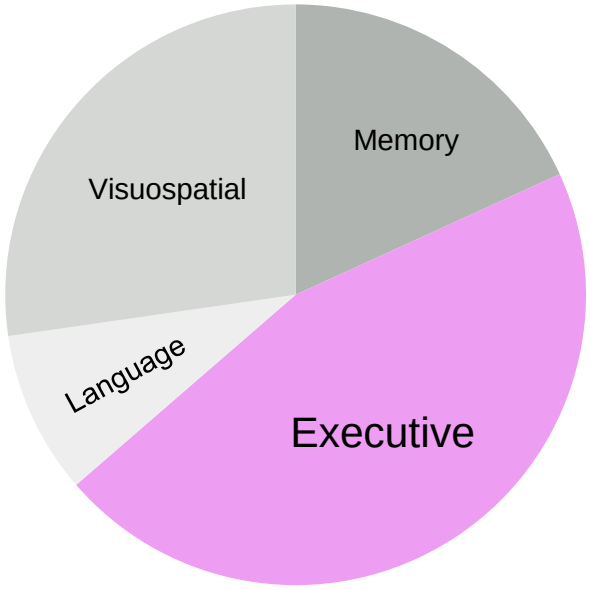
Where Else Do We Find Executive Deficits?

Huntington's Disease*



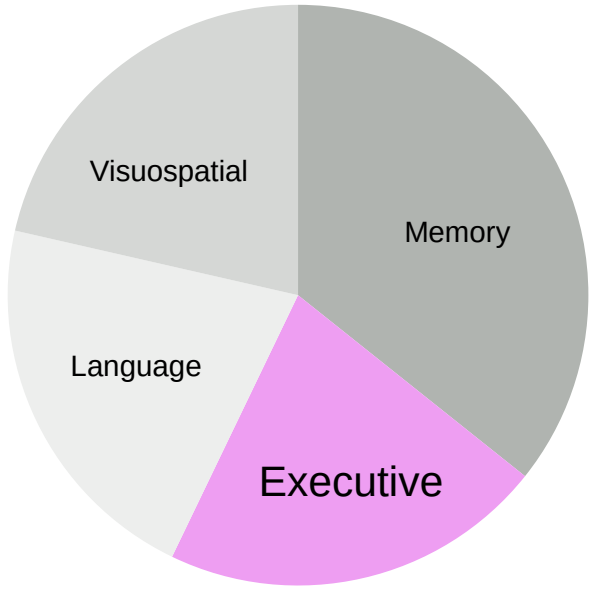
718-CLP-102-B

Parkinson's Disease**



PARADIGM STUDY

Alzheimer's Disease**



LUMINARY Study

*Communication w/ KOL
**Boeve, B. "Mild cognitive impairment associated with underlying Alzheimer's disease versus Lewy body disease." Parkinsonism & Related Disorders, Volume 18, S1, 2012, Pages S41-S44.

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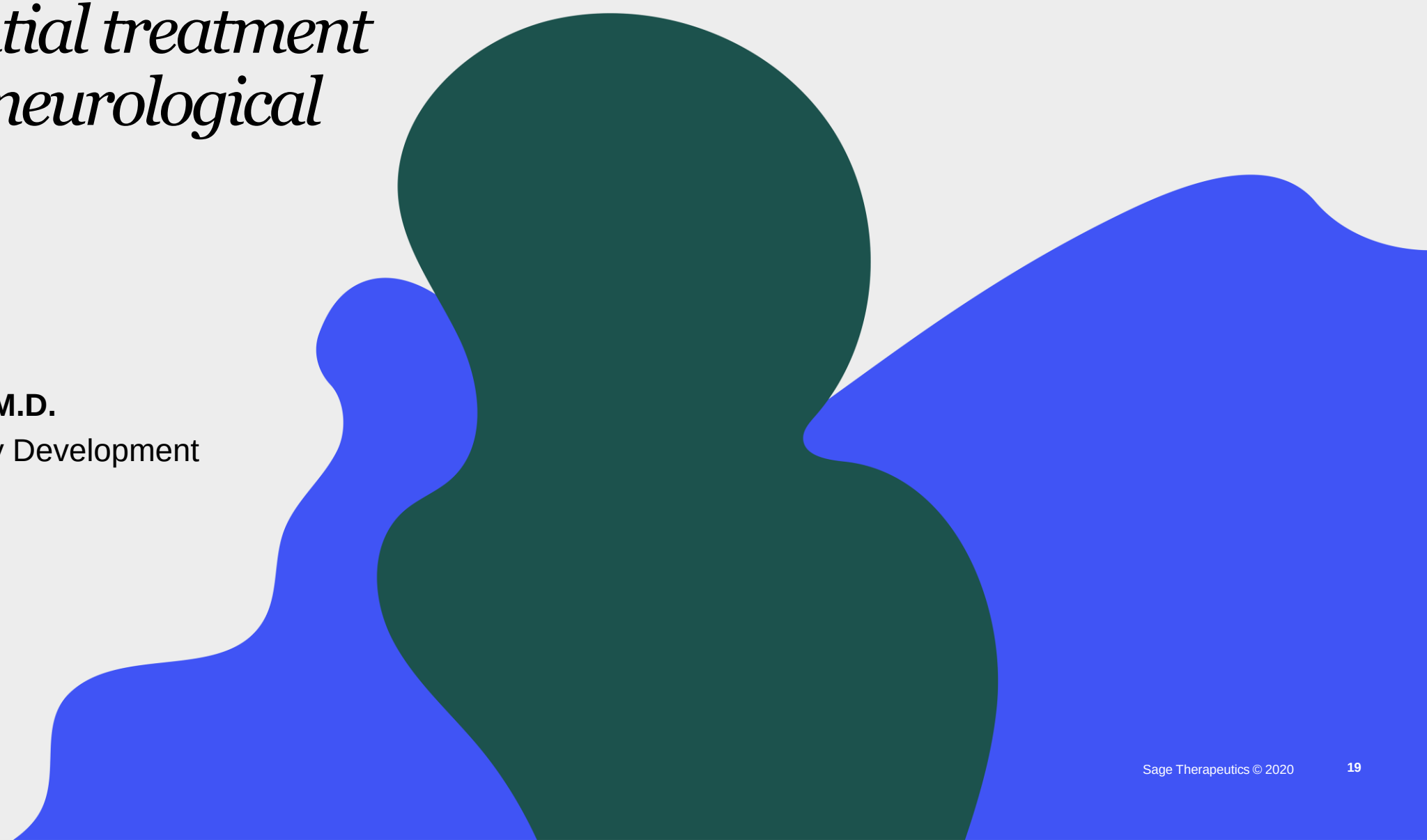
SAGE's NMDA Platform

May provide unique cognitive benefits across therapeutic indications

Findings in healthy volunteers suggest a potential application for cognition beyond illnesses with NMDA hypofunction, with executive function highlighted as a key component of brain health across the lifespan

SAGE-324:
Novel potential treatment for chronic neurological conditions



Helen Colquhoun, M.D.
Vice President, Early Development

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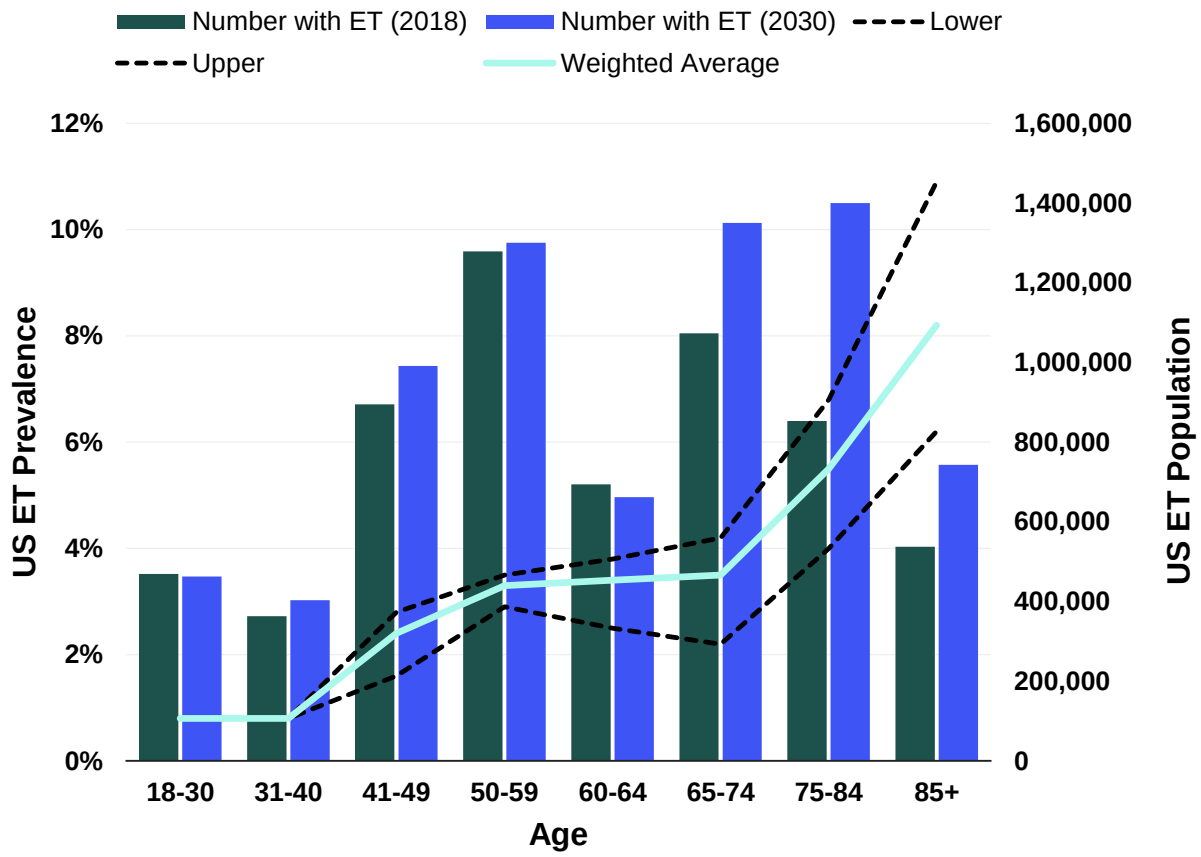
Essential Tremor: Commonest Movement Disorder

- Essential Tremor is the presence of unwanted abnormal movements without other neurological signs
  - Most commonly affects the upper limbs
- In 2018, it was estimated that there were 6.2 million people living with Essential Tremor in the US:
  - ET prevalence increases with age, so this number is projected to grow by 1 million by 2030 as the population ages
  - The true prevalence of Essential Tremor is likely to be underestimated, mainly due to under-diagnosis and mis-diagnosis



Essential Tremor: A Serious Medical Condition

Essential Tremor is progressive, leading to increasing social isolation and loss of independence

Progressively patients (%) experience disability or the need to modify day-to-day activities in the study[1]

74% drinking

69% writing

67% carrying items

66% using a spoon

51% cutting nails

63% of patients report worsening at least every other doctors visit

45% of ET patients reported interference with work or profession[2]

[1]Louis ED, Barnes L, Albert SM, et al. Correlates of Functional Disability in Essential Tremor. Movement Disorder; Vol 16, No. 5. 2001:914-920.
[2]Louis ED, Machado DG. Tremor-related quality of life: A comparison of essential tremor vs. Parkinson's disease patients. Parkinsonism and Related Disorders 2015; 21:729-735.

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Essential Tremor: Unmet Medical Need

- An estimated 60-70% of patients diagnosed with Essential Tremor eventually seek treatment
- First line therapy comprises beta-blockers (60%), anticonvulsants (25%) and a variety of other medications (15%)
- Response to current treatment options is sub-optimal

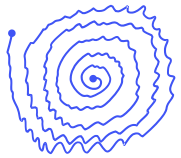
Mild

- Difficulty with very fine motor tasks
- Nervousness about showing a tremor in public
- No caregiver assistance

Approved Treatments:

Propranolol

Moderate



- Difficulty with conducting everyday tasks
- Embarrassment about tremor and withdrawal from social engagements
- Caregiver assistance begins

Approved Treatments:

Propranolol | DBS

Severe

- Significant decline in functioning activities of daily living (ADLs), and independence
- Development of cognitive and psychiatric comorbidities
- Full caregiver involvement

Treatments Involve:

Propranolol | DBS

Abbreviations: DBS = deep brain stimulation

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Essential Tremor: Not Just A Movement Disorder

Substantial Mental Health Impact*

43% report feeling depressed about their Essential Tremor[1]

67% indicated being embarrassed by their Essential Tremor[1]

29% report using alcohol more than they would like because of their Essential Tremor[1]

Substantial Caregiver Burden*

Patients with Essential Tremor rely heavily on caregivers, more so if they have depression or cognitive impairment

56% of caregivers are spouses

29% of caregivers are adult children

*Percentages above are based on % of patients reporting symptom in the study[1]

[1]Louis ED, Machado DG. Tremor-related quality of life: A comparison of essential tremor vs. Parkinson's disease patients. Parkinsonism and Related Disorders 2015; 21:729-735.

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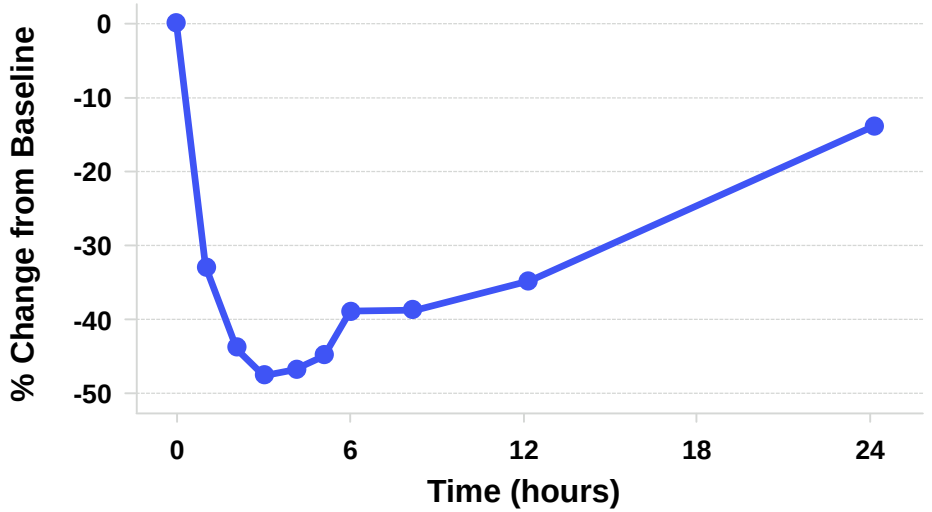
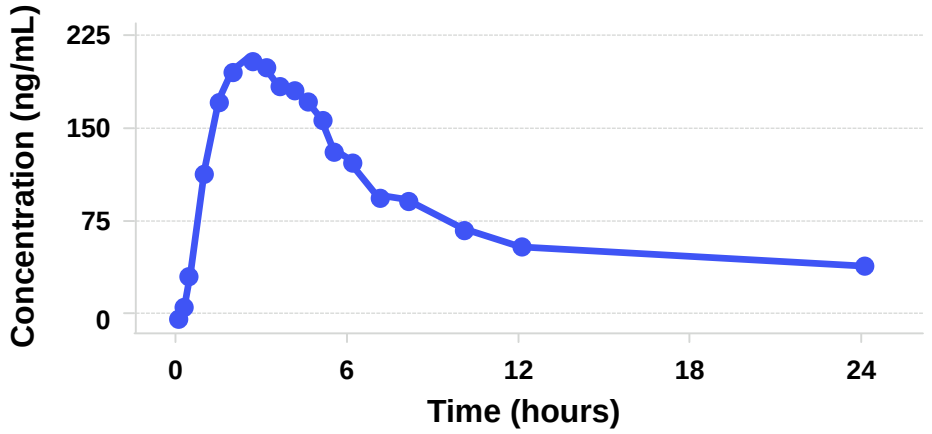
SAGE-324: Strong PK/PD Relationship in ET

- Six patients with essential tremor received a single dose of 60mg SAGE-324
- Tremor amplitude measured using the Kinesia accelerometer and the TETRAS Performance Scale
- A clear PK/PD relationship was demonstrated
- SAGE-324 was well-tolerated in ET patients in the trial

Total upper limb combined score change after SAGE-324 dosing in 6 people with ET as measured by accelerometer



PK over time in 6 people with ET dosed with SAGE-324



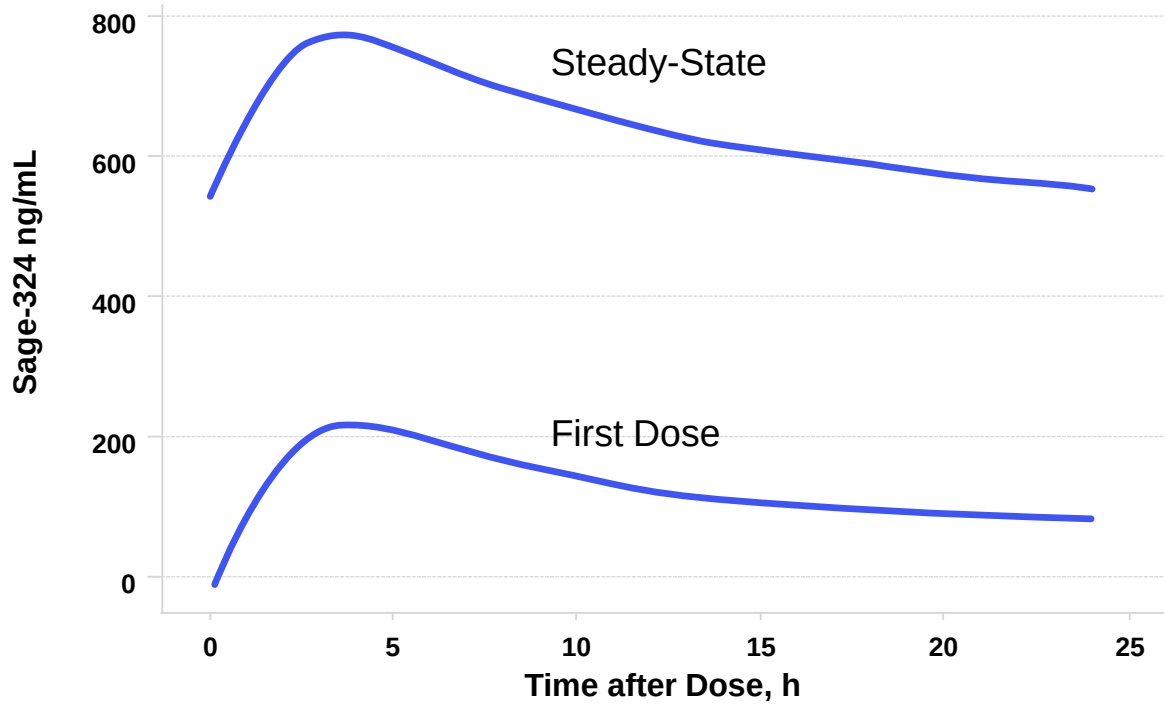
SAGE-324 was well-tolerated in Phase 1 studies; most common AEs (≥5%) included somnolence, dizziness, and feeling of relaxation

SAGE-324: Ability to Maintain Plasma Concentrations Throughout the Dose Interval

SAGE-324 has attributes that support the potential for chronic oral dosing:

- Good oral bioavailability
  - Permits a formulation strategy that optimizes PK profile
- Long half-life
  - Consistent exposures during the dose interval
  - Diminished effect on exposure of missed or late doses
  - Gradual approach to steady state allows potential to facilitate down-titration if tolerability issues arise

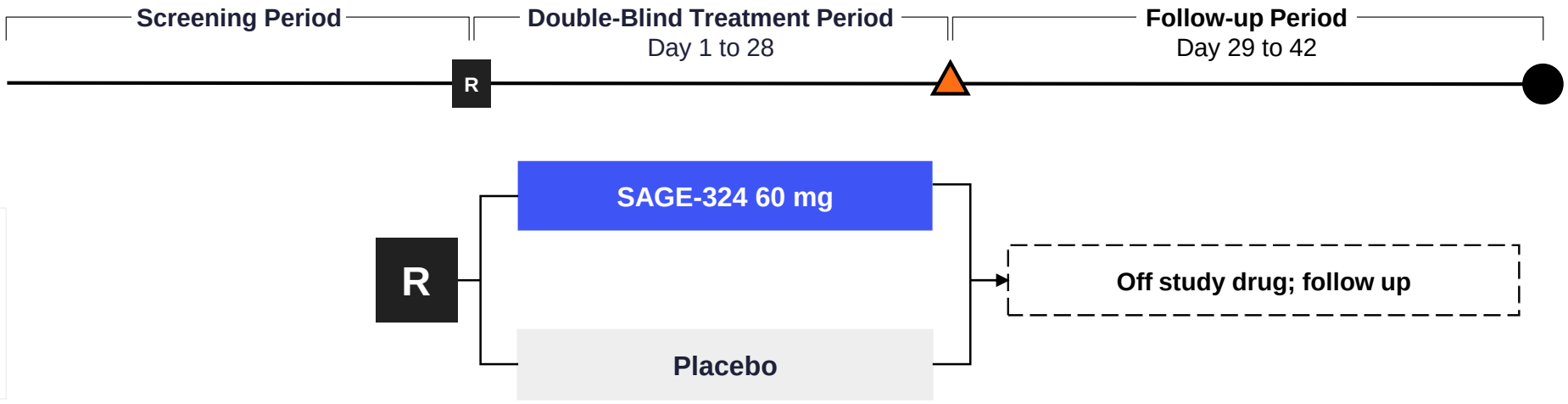
Simulated plasma concentrations following a 60mg daily dose, fed-state



SAGE-324 was well-tolerated in Phase 1 studies; most common AEs (≥5%) included somnolence, dizziness, and feeling of relaxation

A Study to Evaluate the Efficacy, Safety, and Tolerability of SAGE-324 in Participants With Essential Tremor

KINETIC TRIAL



SAGE-324: Early Adoption of Learnings from Other Programs

Learned about the utility and behavior of many endpoints from the brexanolone and zuranolone Essential Tremor studies

Technological endpoints such as accelerometry

Physician reported outcome measures such as CGI

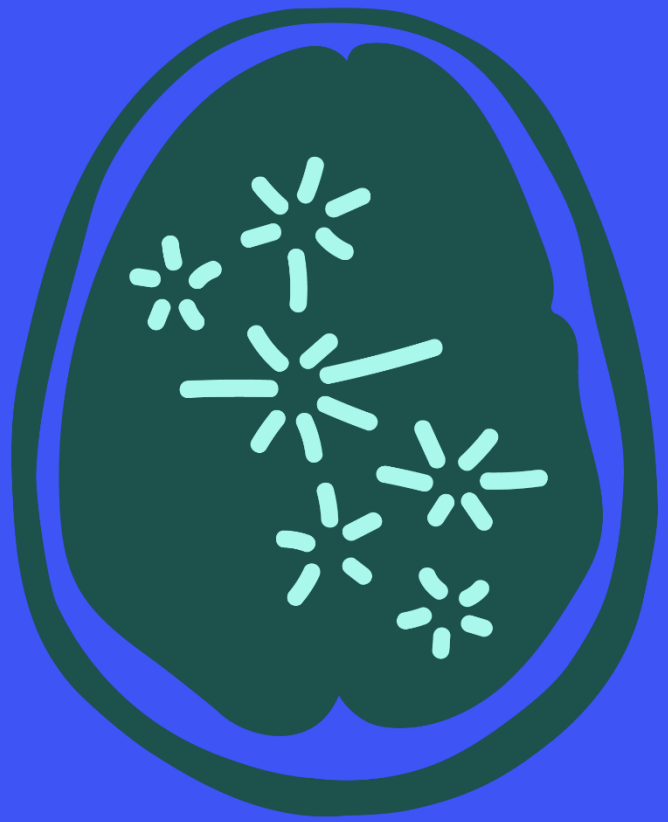
Physician rating scales such as the TETRAS Performance Scale

Patient reported outcome measures such as QUEST

Assessment of activities of daily living such as the TETRAS ADL Scale

SAGE-324: Important Program, Right Time, Right Team

- SAGE-324 has attributes that support potential once daily chronic dosing
- Future dose ranging study planned to define an exposure range and profile with the goal of balancing efficacy and tolerability for patients
- The program is informed by the previous work in Essential Tremor with brexanolone and zuranolone
- Essential Tremor is a serious neurodegenerative condition for which the unmet need is significant
- The SAGE-324 team is executing on schedule despite the COVID-19 pandemic



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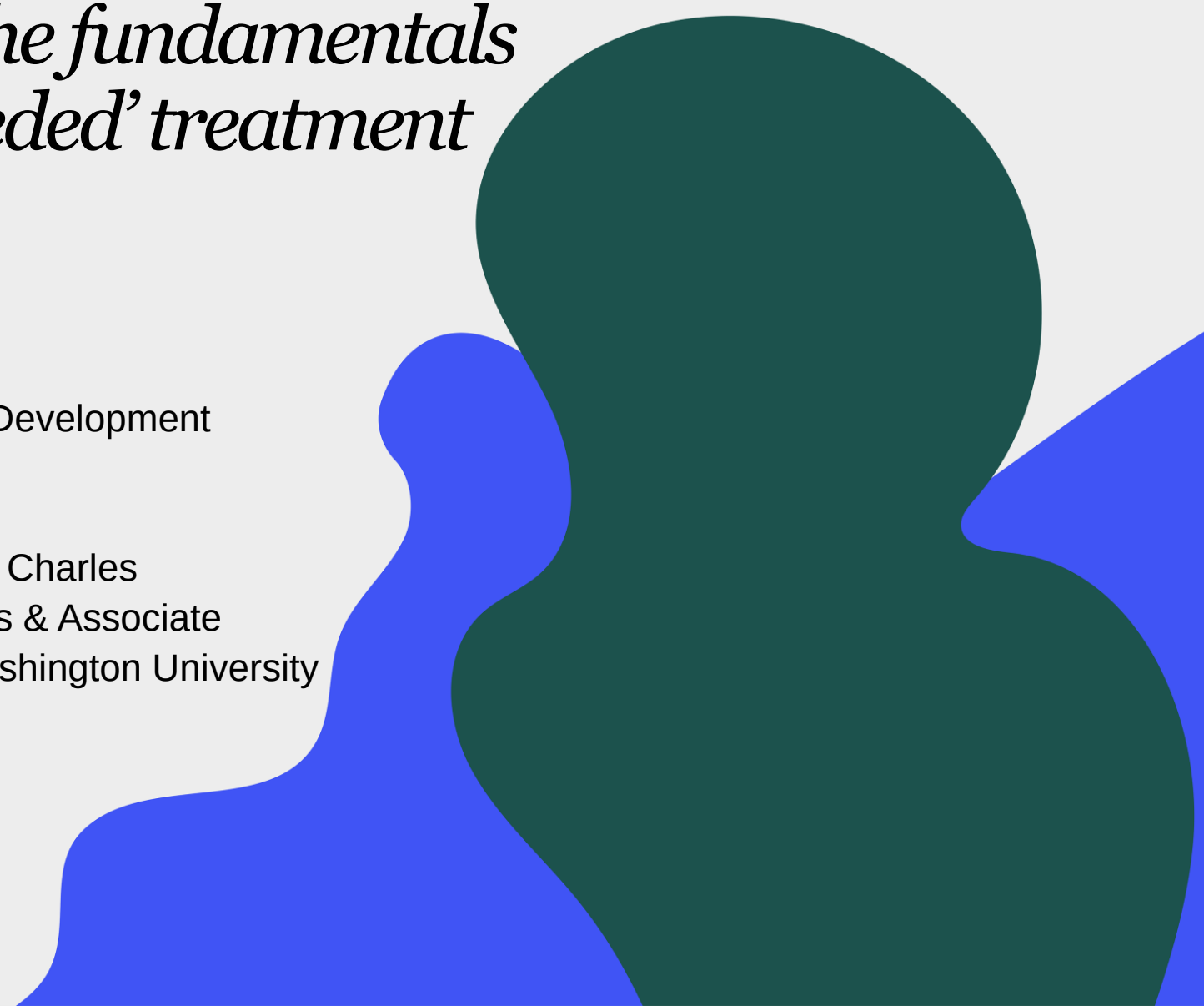
Zuranolone: *Exploring the fundamentals of an 'as needed' treatment in MDD*

Rob Lasser, M.D.
Vice President, Late Development

Greg Mattingly, M.D.
Founding Partner, St. Charles Psychiatric Associates & Associate Clinical Professor Washington University



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Fundamentals of an ‘As Needed’ Treatment

The treatment of MDD is constrained by therapeutic mechanisms of action which require daily medication taking to maintain brain health

- The target profile for zuranolone is linked to this more fundamental GABA mechanism and the potential for two important characteristics: rapid response and sustained effect beyond dosing
  - It is hypothesized that blocking the reuptake of monoamines starts a therapeutic process which ultimately leads to changes in GABA and NMDA signaling which may mediate the ultimate anti-depressant effect
  - This role of monoamine re-uptake blockade may explain the delay in effect of 4 to 6 weeks, and the lack of durability of effect after treatment is stopped
- The vision for zuranolone is linked to this more fundamental GABA mechanism which is thought to underlie two important characteristics: rapid response and sustained effect beyond dosing in most people
  - A treatment must work quickly (within 1 week) to be used ‘as needed’ – cannot require people to endure almost a month to wait for a re-response once MDD recurs
  - A treatment must provide sustained effect in most people to be used ‘as needed’ – would not make sense to stop a medication which works if it does not continue providing benefit beyond the stop of dosing

Dale et al, Biochemical Pharmacology 95 (2015) 81–97

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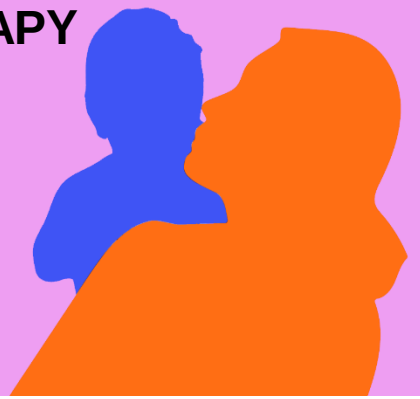
Zuranolone Development Plan

If Successful, Potential to Pursue an Efficient and Expedited Pathway to Filing

Top-line data from studies to support these pathways expected in 2021

MONOTHERAPY
Single course for PPD



- Women with PPD, 14-day course of zuranolone

MONOTHERAPY; ADD-ON in partial response

- People with MDD, 14-day course of zuranolone
- Long term safety data, including from maintenance study, expected to be required for US label

SIMULTANEOUS START
With new ADT for rapid response

- People with MDD, 14-day course of zuranolone

Sage is also currently evaluating the ongoing zuranolone clinical pharmacology and safety program and plans to finalize requirements to support a potential future NDA with the FDA

Dale et al, Biochemical Pharmacology 95 (2015) 81–97

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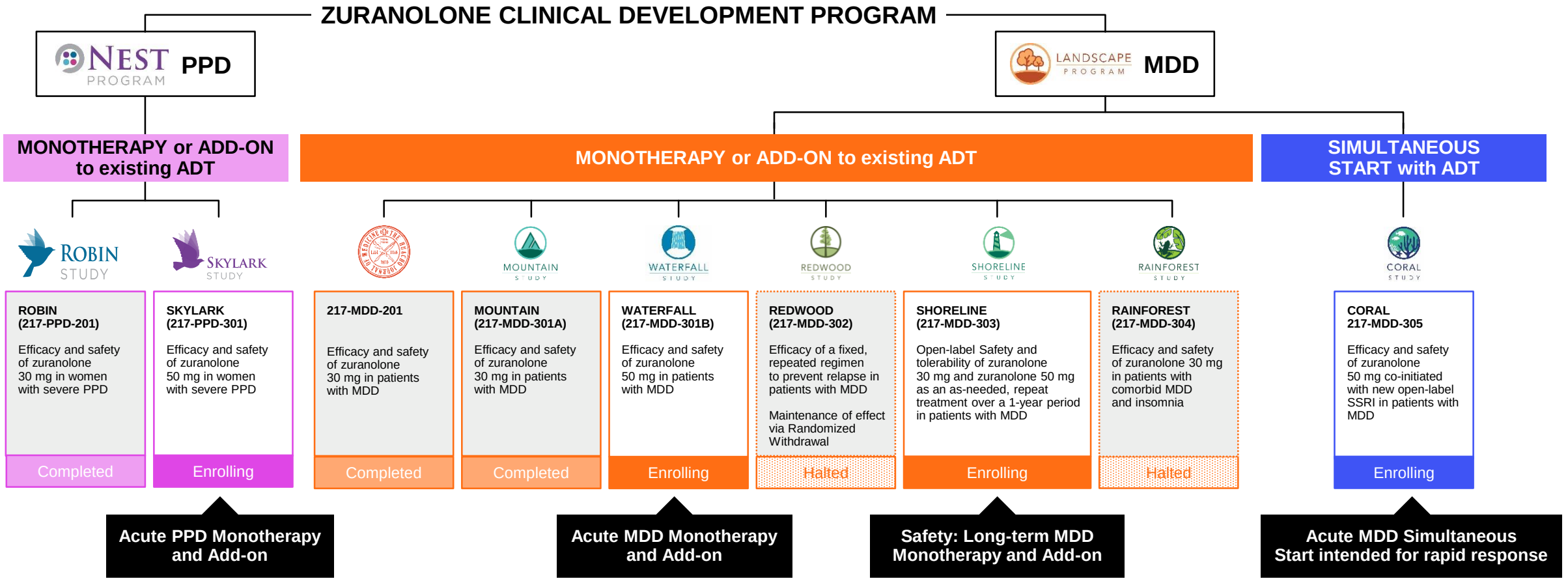
Zuranolone Development Plan

Potential to Pursue an Efficient and Expedited Pathway to Filing



MDD=major depressive disorder; PPD=postpartum depression.

1. Kanes SJ et al. Lancet. 2017;390(10093):480-489. 2. Meltzer-Brody et al. Lancet. 2018;392(10152):1058-1070. 3. Sage Therapeutics, Inc. Data on file. 4. Gunduz-Bruce, et al. N Engl J Med 2019; 381:903-911.

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SHORELINE Study

Focus on experience of initial cohort

- SHORELINE study (MDD-303) design to provide a naturalistic approach to elucidate real-world use patterns, with primary focus on safety of long-term, repeated use
- People with MDD received initial 14-day course of zuranolone, with responders being permitted to continue into full 1-year follow-up with access to all available ADT
- Depression self-assessment every-two-weeks with in-clinic visits every 2 months or as clinically needed

- Approach allows examination of adult and elderly participants using zuranolone:
  - as monotherapy with repeated dosing as needed
  - in conjunction with chronically dosed ADT which are started prior to zuranolone (add on in ‘partial response’)
  - in conjunction with chronically dosed ADT which are started simultaneously with zuranolone
  - in conjunction with chronically dosed ADT which are started after zuranolone course is complete

Conversation with Dr. Greg Mattingly

Dr. Mattingly is an adult and pediatric psychiatrist and an associate Clinical Professor at Washington University in St. Louis, where he received his medical degree under a Fulbright scholarship. As principal investigator in clinical trials for Midwest Research Group and a founding partner of St. Charles Psychiatric Associates, he has executed over 200 clinical trials across multiple Psychiatric disease states.

Zuranolone Program Execution

PPD and MDD programs progressing as planned

NEST PROGRAM

- On track SKYLARK 50 mg (PPD-301; now enrolling)

LANDSCAPE PROGRAM

- On track with
  - WATERFALL (MDD-301B; now enrolling)
  - SHORELINE 50 mg cohort (Now fully enrolled)
  - CORAL 50 mg (MDD-305; planned start 4Q20)
- RAINFOREST on hold as Sage considers examining a 50 mg cohort
- REDWOOD on hold until WATERFALL outcome known
- In SHORELINE, zuranolone 50 mg reported as generally well-tolerated to date, with ~20% down titrating to 40 mg

Brexanolone and COVID-19 related ARDS

Steve Kanes, M.D.
Chief Medical Officer

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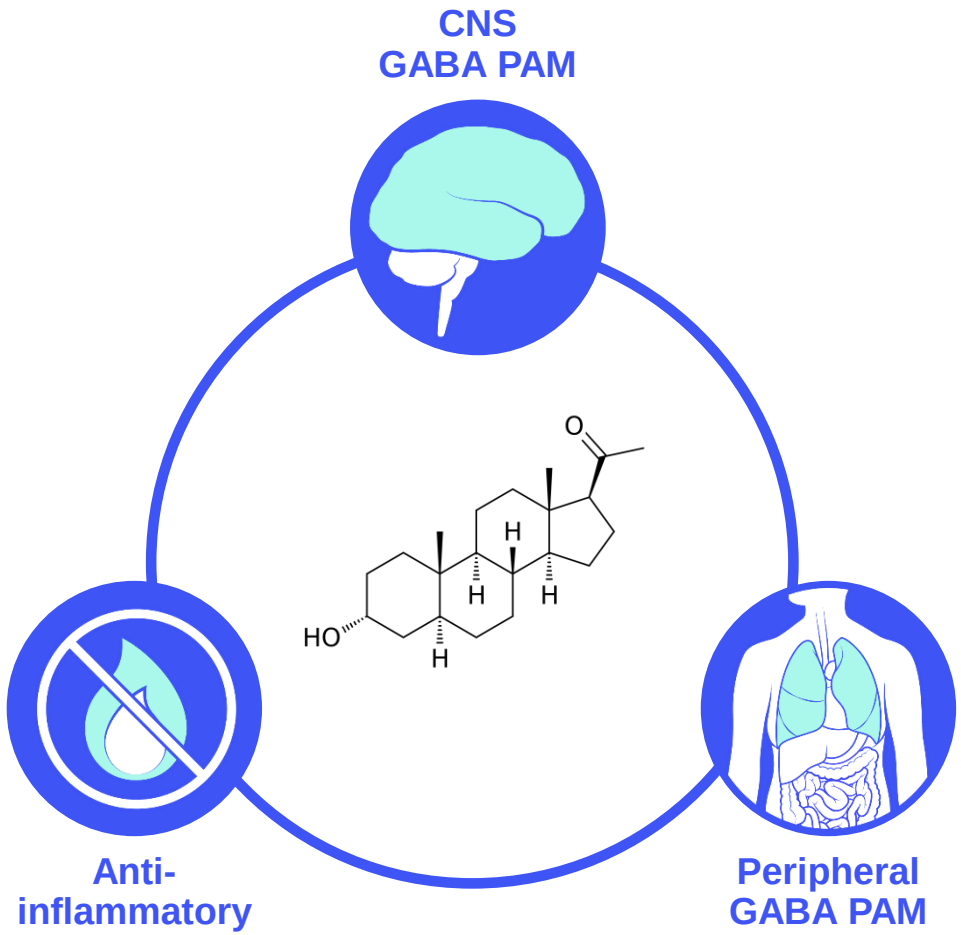
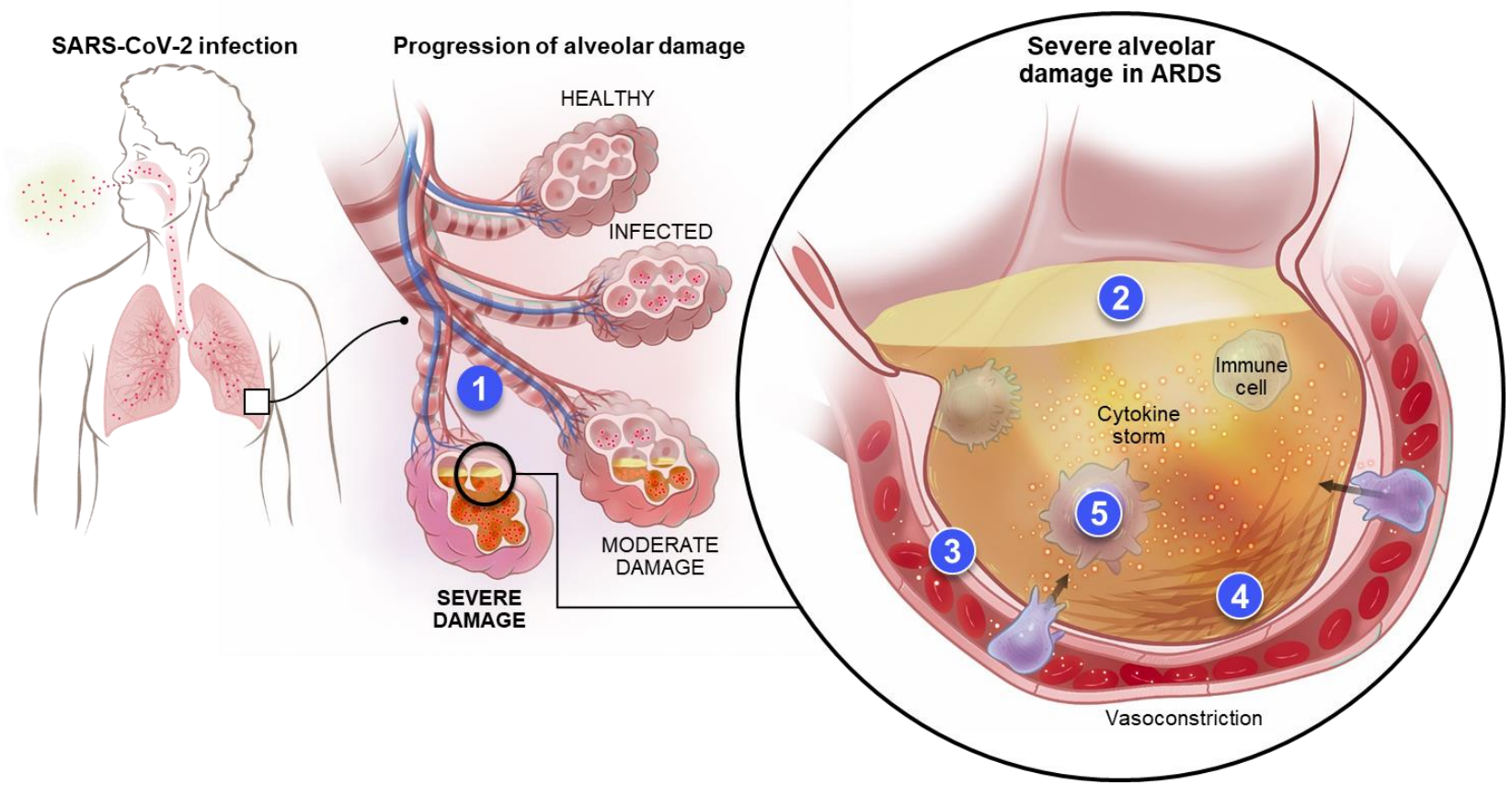
Pleiotropic Pharmacology of Brexanolone



- Peripheral GABA Receptor Modulation
  - Respiratory smooth muscle relaxation
- Anti-inflammatory Activity
  - Emerging pharmacology

Pathophysiology of ARDS in COVID-19 Patients

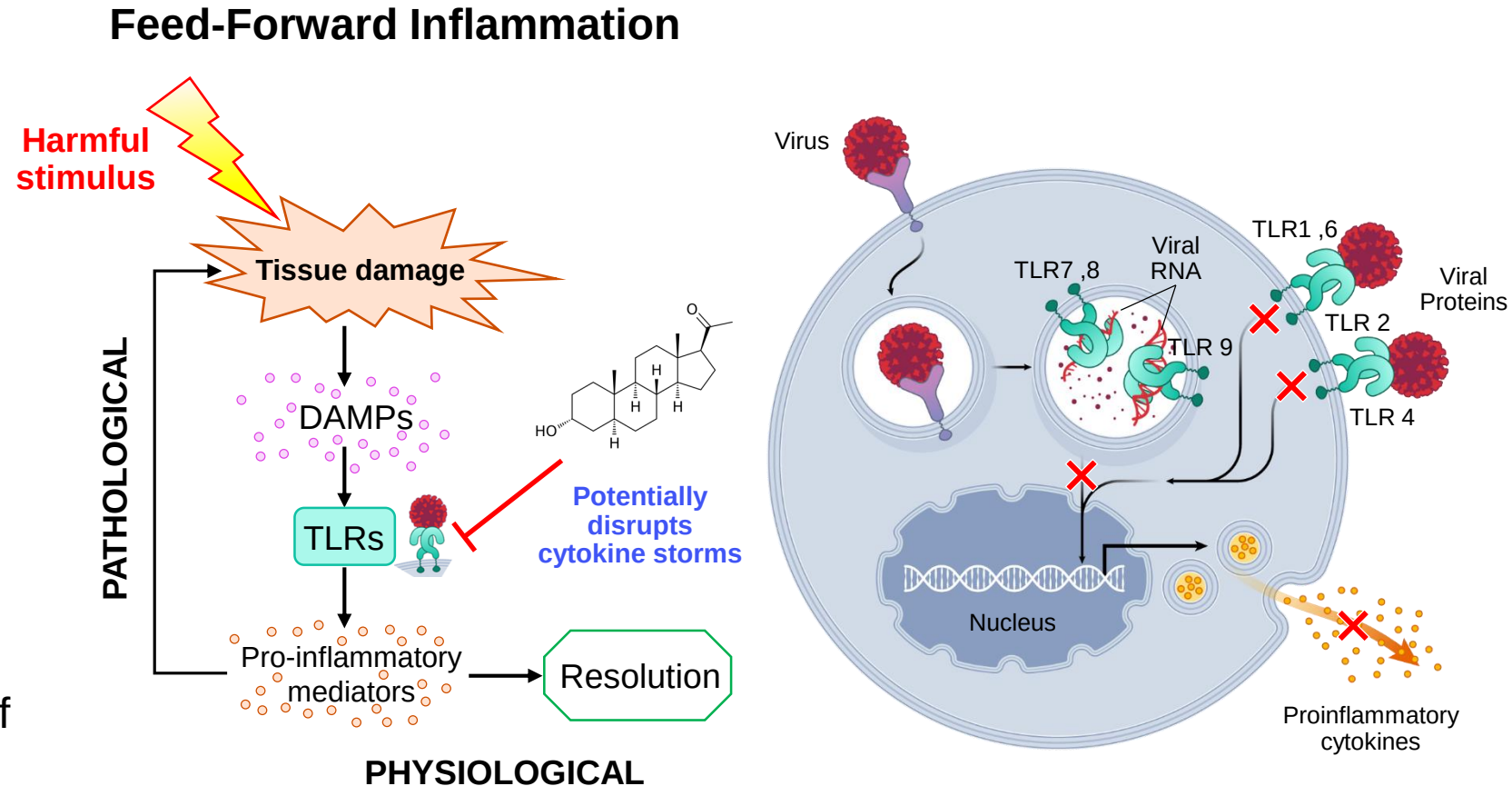


Potential Benefits of GABA PAM and Anti-inflammation Pharmacology

1. Pulmonary smooth muscle relaxation
2. Alveolar fluid clearance
3. Improved gas exchange
4. Reduced fibrotic scarring
5. Disruption of feed-forward inflammation tissue
   - Prevention of cytokine storm and associated tissue damage
   - Reduced immune cell infiltration

Targeting Inflammation with Brexanolone

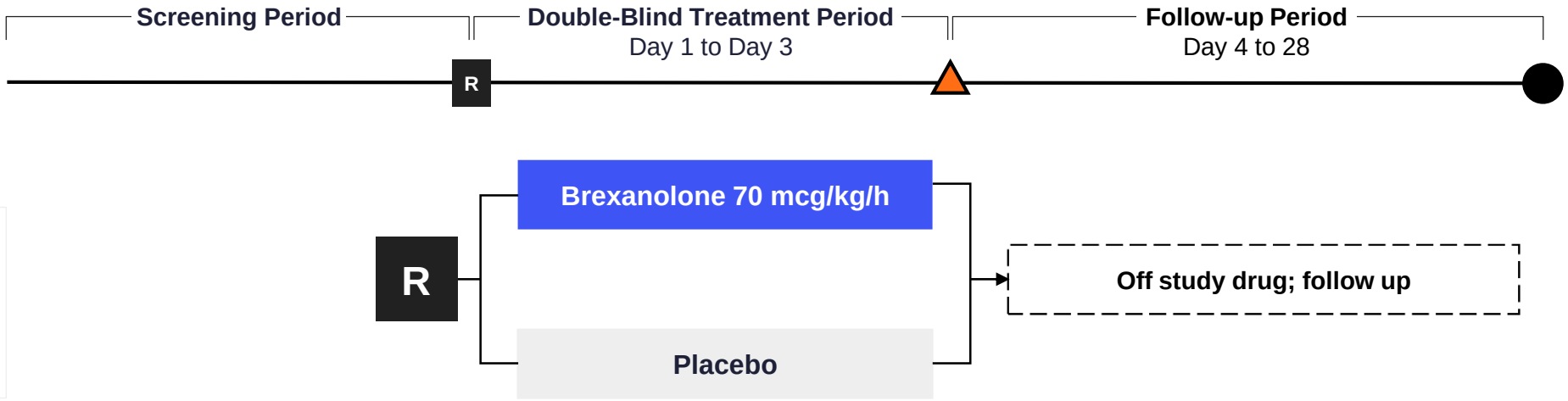
- Emerging evidence supports potential efficacy of brexanolone as an anti-inflammation agent
- Blockade of feed-forward inflammation with goal of:
  - Disruption of ‘cytokine storms’ and prevention of inflammation-induced tissue damage
  - Allows physiological resolution of inflammatory state



Why Study Brexanolone for COVID ARDS?

- Ongoing research, both published and internal data, led to our hypothesis that brexanolone may be effective in treating ARDS
- The pleiotropic pharmacology of brexanolone may reduce inflammation and increase pulmonary smooth muscle relaxation
- We are therefore conducting a study in ventilated patients with COVID-19 related ARDS in the ICU

Clinical Study Design – ARDS Due to COVID-19



STUDY OVERVIEW			
Indication	ARDS due to COVID-19	**Inclusion Criteria**	• Positive for SARS-CoV-2 • ARDS • Intubated and receiving mechanical ventilation for <48 hours at screening
Phase	3	**Primary Endpoint**	• Percentage of subjects alive and free of respiratory failure at Day 28
Arms	Double-blind, randomized:1:1 • Brexanolone 70 mcg/kg/h • Placebo	**Secondary Endpoints**	• Treatment-emergent adverse events • All-cause mortality through Day 28
Dosing Regimen	60 Hour Continuous IV Infusion	**Additional Endpoints**	• Respiratory parameters • Change in cytokines and inflammatory markers • Changes in anesthetic dose

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Summary

- Due to potential in treating COVID-19-related ARDS and extensive experience in an ICU setting, in the face of an ongoing global health crisis Sage has responsibility to investigate
- Study will add to understanding of potential utility of brexanolone for respiratory function, as well as its role in inflammation
- Data from this study will be useful for our internal decision making for strategic pipeline planning

Conclusion

Jeff Jonas, M.D.
Chief Executive Officer

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Seeing the brain differently *makes a world of difference*

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