Sage Therapeutics Announces Second Quarter 2021 Financial Results and Highlights Pipeline and Business Progress

August 3, 2021

Announced positive topline data from pivotal WATERFALL Study of zuranolone in patients with MDD showing statistically significant and clinically meaningful reduction in depressive symptoms at Day 15, primary endpoint

Continued pipeline expansion and acceleration advancing all three brain health franchises, including first patient dosed in SAGE-718 PARADIGM Parkinson's disease Study Part B and initiation of Phase 1 program for SAGE-689

Updated enrollment guidance for Phase 3 SKYLARK Study of zuranolone in women with PPD with topline data now expected mid-2022

Company announces REDWOOD and RAINFOREST Studies not expected to be required for a potential zuranolone NDA submission

Conference call today at 8:00 a.m. ET

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Aug. 3, 2021-- Today, Sage Therapeutics, Inc. (Nasdaq: SAGE), a biopharmaceutical company committed to developing novel therapies with the potential to transform the lives of people with debilitating disorders of the brain, reported business highlights and financial results for the second quarter ended June 30, 2021.

"Sage has made incredible progress on our mission to become the leader in brain health in the first half of 2021, setting us up for multiple near-mid and long-term catalysts." said Barry Greene, chief executive officer, Sage Therapeutics. "Our goal of making medicines that matter for people with brain health disorders is more important than ever, and we are committed to delivering innovative therapies. The LANDSCAPE and NEST programs for zuranolone are examples of Sage's unique approach to designing integrated clinical development strategies that we believe will enable us to bring paradigm shifting treatments to market and address the greatest unmet needs for patients. I look forward to providing further updates on zuranolone and the rest of Sage's robust pipeline in the second half of the year."

Second Quarter 2021 and Recent Portfolio Updates

Sage is advancing a portfolio of clinical programs featuring internally discovered novel chemical entities with the potential to become differentiated products designed to improve brain health by targeting the $GABA_A$ and NMDA receptor systems. Dysfunction in these systems is thought to be at the core of numerous neurological and neuropsychiatric disorders.

Depression Franchise

Sage's depression franchise features zuranolone, Sage's next-generation positive allosteric modulator (PAM) of $GABA_A$ receptors being evaluated in clinical development as a treatment for various affective disorders, and ZULRESSO® (brexanolone) CIV injection, approved by the U.S. Food and Drug Administration (FDA) as the first treatment specifically indicated for postpartum depression (PPD). Zuranolone has received breakthrough therapy designation from the FDA for the treatment of major depressive disorder (MDD).

Zuranolone is being evaluated as a potential rapid-acting, durable, two-week treatment for PPD and MDD in the NEST and LANDSCAPE clinical trial programs.

Sage and Biogen, its collaborator on zuranolone and SAGE-324, recently announced that the WATERFALL Study, a pivotal, Phase 3, double-blind, randomized, placebo-controlled study evaluating the efficacy and safety of zuranolone 50 mg in adults 18 to 64 years with MDD, met its primary endpoint demonstrating statistically significant and clinically meaningful improvement in depressive symptoms compared with placebo at Day 15 as assessed by the 17-item Hamilton Rating Scale for Depression (HAMD-17) total score.

- The WATERFALL Study enrolled 543 patients with MDD; patients were treated with zuranolone 50 mg or placebo once nightly for 14 days.
- The mean (SD) baseline HAMD-17 score at entry into the study was 26.8 (2.60) in the zuranolone 50 mg treatment group (n=268) and 26.9 (2.67) in the placebo group (n=269).
- 90.3% of patients who received zuranolone, and 87.4% of patients who received placebo, completed the study.
- The LS means (SE) change from baseline in HAMD-17 total score at Day 15 for patients who received zuranolone 50 mg was -14.1 (0.51) compared with -12.3 (0.50) for patients who received placebo (LS mean difference -1.7 points; p=0.0141).
- Rapid and significant onset of treatment effect was also seen in HAMD-17 results at Days 3, 8, and 12.
- Patients with a response to zuranolone at Day 15 retained on average 86% of their HAMD-17 improvement at Day 42 (4 weeks after dosing ended).
- Zuranolone was generally well-tolerated in the WATERFALL Study and demonstrated a safety profile consistent with previous clinical studies. The most common treatment-emergent adverse events (TEAEs) that were ≥ 5% in patients treated with zuranolone (rates vs placebo) included somnolence 15.3% (vs 3.0%), dizziness 13.8% (vs 2.2%), headache

10.8% (vs 7.8%), and sedation 7.5% (vs 0.4%); these events predominantly occurred during the 14-day treatment period.
    - There were no reports of weight gain, sexual dysfunction, euphoria or nausea typically associated with most, if not all, antidepressant drugs.

Zuranolone has been granted Breakthrough Therapy Designation by the FDA, and Sage and Biogen plan to discuss next steps with the Agency. Additional analysis and full data from the WATERFALL Study will be shared at future scientific forums.

Additionally, the Company is formally terminating the REDWOOD and RAINFOREST Studies, which were suspended in the first quarter of 2020. After discussions with the FDA, Sage does not believe that these studies will be required for a potential NDA submission.

The Company expects the following zuranolone data readouts in 2021 and 2022:

- Late 2021:
    - CORAL (MDD-305) Study: A placebo-controlled Phase 3 trial evaluating a two-week course of zuranolone 50 mg, when co-initiated with a new antidepressant, in patients with MDD, with additional short-term follow-up.
    - SHORELINE (MDD-303) Study 50 mg Cohort (1-year data cut): An open-label Phase 3 trial designed to naturalistically follow patients with MDD and evaluate the safety and tolerability of zuranolone 50 mg in adults for up to one year. The Company announced interim data from the 50 mg treatment cohort in March 2021.

- Mid-2022:
    - SKYLARK (PPD-301) Study: A placebo-controlled Phase 3 trial evaluating a two-week course of zuranolone 50 mg in women with PPD, with additional short-term follow-up.
        - Sage now expects topline data for the SKYLARK Study in mid-2022, because of a slower than anticipated pace of enrollment in the study, due to a lower number of women seeking care for PPD and a lower rate of childbirth during the pandemic.

Sage today announced topline data from the Phase 3 CHICKADEE Study evaluating the safety of ZULRESSO treatment in adolescent females aged 15 to 17 with postpartum depression. This study was conducted as a post-marketing requirement to investigate ZULRESSO in an adolescent population diagnosed with PPD. In the study, the safety and pharmacokinetic profile of ZULRESSO in this population was consistent with prior studies in adults and the FDA-approved product label. While not the primary endpoint, efficacy results were positive and consistent with previous studies.

Neurology Franchise

SAGE-324, a next-generation PAM of $GABA_A$ receptors and Sage's lead neurology program, is in development as a potential oral therapy for neurological conditions, such as essential tremor (ET), epilepsy and Parkinson's disease (PD).

In the second quarter, Sage and Biogen announced that the KINETIC Study, a Phase 2 multicenter, randomized, double-blind, placebo-controlled study of SAGE-324 in ET, met its primary endpoint.

- In the study, SAGE-324 demonstrated a statistically significant reduction from baseline in the TETRAS Item 4 upper limb tremor score at Day 29 in the total studied population compared to placebo.
- Also in the study, SAGE-324 demonstrated a statistically significant correlation between TETRAS tremor score and activities of daily living at all measured time points.
- Sage and Biogen anticipate initiating a Phase 2 dose-ranging study in late 2021, with the goal of optimizing the dose and frequency, including to maintain plasma concentrations that translate into sustained tremor symptom control.

Neuropsychiatry Franchise

SAGE-718, Sage's first-in-class NMDA receptor PAM and lead neuropsychiatric drug candidate, is in development as a potential oral therapy for cognitive disorders associated with NMDA receptor dysfunction, potentially including Huntington's disease (HD), PD and Alzheimer's disease (AD).

This quarter, Sage dosed the first patient in the 4-week dosing cohort, or part B, of the PARADIGM Study to gather additional data on SAGE-718 in the PD patient population. The PARADIGM Study is a Phase 2a open-label study in patients aged 50 to 75 years old with mild cognitive impairment due to PD. Additionally, the LUMINARY Study, a Phase 2a open-label trial evaluating SAGE-718 in patients with AD mild cognitive impairment and mild dementia is ongoing.

The following milestones are expected for the neuropsychiatry franchise in 2021:

- Late 2021:
    - LUMINARY (718-CNA-201) Study**:** The Company anticipates topline data from the LUMINARY Study in late 2021.
    - Phase 2 Study in HD: The Company expects to initiate a placebo-controlled Phase 2 trial with SAGE-718 in early to moderate HD in late 2021.

Early Development

Sage expects to complete certain ongoing Phase 1 clinical studies for two programs in its early development pipeline in late 2021, SAGE-689 (single ascending dose) and SAGE-904 (single ascending dose and multiple ascending dose). Results from the Phase 1 studies will inform further development of these programs.

- **SAGE-689:** an intramuscular $GABA_A$ receptor PAM in development as a potential therapy for disorders associated with acute GABA hypofunction. In the second quarter, the first patient was dosed in the SAGE-689 Phase 1 SAD study.
- **SAGE-904:** Sage's second NMDA receptor PAM product candidate in development as a potential oral therapy for disorders associated with NMDA hypofunction. In the second quarter, the first patient was dosed in the continued SAGE-904 Phase 1 studies.

Additionally, IND-enabling work is underway for SAGE-319.

- **SAGE-319:** an oral, extrasynaptic $GABA_A$ receptor preferring PAM that Sage plans to study for potential use in disorders of social interaction.

The Company plans to advance SAGE-421 to preclinical studies.

- **SAGE-421:** an oral, NMDA receptor PAM that Sage plans to study for potential use in neurodevelopmental disorders and cognitive recovery and rehabilitation.

Other Development Opportunities

Sage's Phase 3 trial with brexanolone in ventilated intensive care unit patients with advanced COVID-19 related acute respiratory distress syndrome (ARDS) did not meet enrollment expectations and was closed to enrollment this quarter. Sage has terminated the study.

ANTICIPATED 2021 MILESTONES

Late 2021:

- Zuranolone:
  - Report topline data from Phase 3 CORAL Study
  - Report topline data cut from Phase 3 SHORELINE Study 50 mg cohort
- SAGE-324:
  - Initiate Phase 2 dose-ranging study in ET
- SAGE-718:
  - Report topline data from Phase 2a LUMINARY open-label, signal finding study in patients with AD mild cognitive impairment and mild dementia
  - Initiate placebo-controlled Phase 2 study in early to moderate HD
- SAGE-689 & SAGE-904:
  - Complete ongoing Phase 1 studies (SAD for SAGE-689 and SAD/MAD for SAGE-904)

FINANCIAL RESULTS FOR THE SECOND QUARTER 2021

- **Cash Position:** Cash, cash equivalents and marketable securities as of June 30, 2021 were $1.9 billion compared to $2.0 billion at March 31, 2021.
- **Revenue:** Net revenue from sales of ZULRESSO was $1.6 million in the second quarter of 2021 compared to $1.1 million in the same period of 2020.
- **R&D Expenses:** Research and development expenses were $66.2 million, including $13.5 million of non-cash stock-based compensation expense, in the second quarter of 2021 compared to $73.3 million, including $10.1 million of non-cash stock-based compensation expense, for the same period in 2020, a decrease of $7.1 million. The amount for the second quarter of 2021 reflects an increase in expenses of $13.0 million and a reduction in expenses of $20.1 million due to reimbursement from Biogen pursuant to the Sage/Biogen Collaboration and License Agreement. The primary reasons for the increase in expenses were clinical pharmacology studies that began in 2021 and non-cash stock-based compensation expense from the achievement of a milestone for certain outstanding performance restricted stock units.
- **SG&A Expenses:** Selling, general and administrative expenses were $43.3 million, including $14.2 million of non-cash stock-based compensation expense, in the second quarter of 2021 compared to $38.2 million, including $12.1 million of non-cash stock-based compensation expense, for the same period in 2020, an increase of $5.1 million. The amount for the second quarter of 2021 reflects an increase in expenses of $8.6 million and a reduction in expenses of $3.5 million due to reimbursement from Biogen pursuant to the Sage/Biogen Collaboration and License Agreement. The primary reasons for the increase in expenses were an increase in activities focused on disease awareness, increased launch readiness activities for a potential product launch, if our zuranolone development efforts are successful, and non-cash stock-based compensation expense from the achievement of a milestone for certain outstanding performance restricted stock units.
- **Restructuring Expenses:** Sage had no restructuring expenses in the second quarter of 2021 compared to $28.4 million in

the second quarter of 2020.

- **Net Loss:** Net loss was $107.2 million for the second quarter of 2021 compared to a net loss of $136.3 million for the same period in 2020.

FINANCIAL GUIDANCE

- Sage anticipates cash, cash equivalents, and marketable securities of more than $1.7 billion at end of 2021.
- The Company does not anticipate receipt of any milestone payments from collaborations in 2021.

Conference Call Information

Sage will host a conference call and webcast today, Tuesday, August 3, at 8:00 am ET to discuss its second quarter 2021 financial results and recent corporate updates. The live webcast can be accessed on the investor page of Sage's website at investor.sagerx.com. A replay of the webcast will be available on Sage's website approximately two hours after the completion of the event and will be archived for up to 30 days.

About Sage Therapeutics

Sage Therapeutics is a biopharmaceutical company committed to developing novel therapies with the potential to transform the lives of people with debilitating disorders of the brain. We are pursuing new pathways with the goal of improving brain health, and our depression, neurology and neuropsychiatry franchise programs aim to change how brain disorders are thought about and treated. Our mission is to make medicines that matter so people can get better, sooner. For more information, please visit www.sagerx.com.

Forward-Looking Statements

Various statements in this release concern Sage's future expectations, plans and prospects, including without limitation: our views and expectations regarding our planned research and development activities and related timelines, including anticipated timelines for reporting clinical trial results, commencement of trials, and initiation of new activities; our plans for advancement of our pipeline; our belief in the potential profile and benefit of our product candidates, the potential for our programs, and the opportunity to help patients in various indications; our belief and expectations as to the potential regulatory pathways and requirements for filing a potential new drug application for zuranolone and for possible approval; potential indications for our product candidates; the mission and goals for our business and potential value creation opportunities; and our expectations with respect to 2021 year-end cash. These statements constitute forward-looking statements as that term is defined in the Private Securities Litigation Reform Act of 1995. 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 risks that: success in non-clinical studies or in earlier clinical trials or at interim time periods may not be repeated or observed in ongoing or future studies, and ongoing and future non-clinical and clinical results may not meet their primary or key secondary endpoints or be sufficient to file for or gain regulatory approval to market the product without further development work or may not support further development at all; unexpected concerns may arise from additional data, analysis or results from any of our completed studies; we may encounter adverse events at any stage of development that negatively impact further development or that require additional nonclinical and clinical work which may not yield positive results; we may encounter delays in initiation, conduct or completion of our ongoing and planned clinical trials, including as a result of slower than expected site initiation or enrollment, the need or decision to expand the trials or other changes, that may impact our ability to meet our expected timelines and increase our costs; the impact of the COVID-19 pandemic on our clinical development efforts may be more significant than we expect if new surges continue; the FDA may ultimately decide that the design or results of our completed, ongoing and planned clinical trials for zuranolone or any of our other 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 even if we have had prior discussions with the agency supporting our approach; 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; the anticipated benefits of our ongoing collaborations may never be achieved and the need to align with our collaborators may hamper or delay our development and commercialization efforts or increase our costs; our business may be adversely affected and our costs may increase if any of our key collaborators fails to perform its obligations or terminates our collaboration; 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; we may never be able to generate meaningful revenues from sales of ZULRESSO or to generate revenues at levels we expect or at levels necessary to justify our investment; 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; our expectations as to year-end cash may prove not to be correct for other reasons such as changes in plans or actual events being different than our assumptions; we may be opportunistic in our future financing plans even if available cash is sufficient; additional funding may not be available on acceptable terms when we need it; the number of patients with the diseases or disorders for which our products are developed, the unmet need for additional treatment options and the potential market for our current or future products may be significantly smaller than we expect; and we may encounter technical and other unexpected hurdles in the development and manufacture of our product candidates or the commercialization of our marketed product which may delay our timing or change our plans, increase our costs or otherwise negatively impact our business; as well as those risks more fully discussed in the section entitled "Risk Factors" in our most recent Quarterly Report on Form 10-Q, as well as discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent our views only as of today, and should not be relied upon as representing our views as of any subsequent date. We explicitly disclaim any obligation to update any forward-looking statements.

Sage Therapeutics, Inc. and Subsidiaries
Condensed Consolidated Statements of Operations
(in thousands, except share and per share data)
(unaudited)

	Three Months Ended June 30,		Six Months Ended June 30,	
	2021	2020	2021	2020

Product revenue, net	$ 1,643	$ 1,089	$ 3,226	$ 3,375
Operating costs and expenses:				
Cost of goods sold	148	110	335	280
Research and development	66,170	73,320	124,226	136,930
Selling, general and administrative	43,346	38,224	83,193	108,355
Restructuring	-	28,402	-	28,402
Total operating costs and expenses	109,664	140,056	207,754	273,967
Loss from operations	(108,021)	(138,967)	(204,528)	(270,592)
Interest income, net	732	2,686	1,440	7,416
Other income (expense), net	44	(66)	79	89
Net loss	$ (107,245)	$ (136,347)	$ (203,009)	$ (263,087)
Net loss per share - basic and diluted	$ (1.83)	$ (2.63)	$ (3.47)	$ (5.07)
Weighted average shares outstanding - basic and diluted	58,582,569	51,926,074	58,478,970	51,917,417

Sage Therapeutics, Inc. and Subsidiaries
Condensed Consolidated Balance Sheets
(in thousands)
(unaudited)

	June 30, 2021	December 31, 2020
Cash, cash equivalents and marketable securities	$1,911,315	$ 2,099,549
Total assets	$2,015,475	$ 2,159,246
Total liabilities	$ 85,963	$ 86,912
Total stockholders' equity	$1,929,512	$ 2,072,334

ZULRESSO can cause serious side effects, including:

- **Excessive sedation and sudden loss of consciousness.** ZULRESSO may cause you to feel very sleepy (excessive sedation) or pass out (loss of consciousness). Your healthcare provider should check you for symptoms of excessive sleepiness every 2 hours while you are awake.
  - During your infusion, tell your healthcare provider right away if you feel like you cannot stay awake during the time you are normally awake or if you feel like you are going to pass out. Your healthcare provider may lower your dose or stop the infusion until symptoms go away.
  - You must have a caregiver or family member with you to help care for your child(ren) during your infusion.
- Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness, ZULRESSO is only available through a restricted program called the ZULRESSO REMS.

ZULRESSO can cause other serious side effects, including:

- **Increased risk of suicidal thoughts or actions.** ZULRESSO and other antidepressant medicines may increase suicidal thoughts and actions in some people 24 years of age and younger. **Pay close attention to and tell your healthcare provider right away if you have any of the following symptoms, especially if they are new, worse, or worry you:**
  - Attempts to commit suicide, thoughts about suicide or dying, new or worse depression, other unusual or sudden changes in behavior or mood.
  - Keep all follow-up visits and call your healthcare provider between visits as needed, especially if you have concerns about symptoms.

The most common side effects of ZULRESSO include:

- Sleepiness, dry mouth, passing out, flushing of the skin or face.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Before receiving ZULRESSO, tell your healthcare provider about all your medical conditions including if you drink alcohol, have kidney problems, are pregnant or think you may be pregnant, or are breastfeeding or plan to breastfeed. It is not known if ZULRESSO will harm your unborn baby. If you become pregnant during treatment, talk with your healthcare provider about enrolling with the National Pregnancy Registry for Antidepressants at 1-844-405-6185.

While receiving ZULRESSO, avoid the following:

- Driving a car or doing other dangerous activities after your ZULRESSO infusion until your feeling of sleepiness has

completely gone away.
- Do not drink alcohol.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ZULRESSO and some medicines may interact with each other and cause serious side effects.

Especially tell your healthcare provider if you take other antidepressants, opioids, or Central Nervous System (CNS) depressants (such as benzodiazepines).

Please see the patient Medication Guide, including information about serious side effects, for ZULRESSO in the full Prescribing Information.

View source version on businesswire.com: https://www.businesswire.com/news/home/20210803005320/en/

Investor Contact
Jeff Boyle
347-247-5089
jeff.boyle@sagerx.com

Media Contact
Maureen L. Suda
617-949-4289
maureen.suda@sagerx.com

Source: Sage Therapeutics, Inc.