Sea Pharmaceuticals Announces Strategic Relationship to Advance Treatments For Patients with CNS Disorders

- *Sea's pre-clinical stage neurotherapeutic synthetic oral molecules act at the neurotransmitter glutamate pathway on two clinically validated targets in the CNS (central nervous system)*
- *Sea's lead molecule SPM-0404 is a potential new oral treatment in investigational new drug (IND)-enabling studies for constant bothersome tinnitus, epilepsy, and sporadic ALS (S-ALS)*
    - *Pre-clinical development work by Inotiv, Inc. to support Sea filing IND application at FDA*
    - *Inotiv Inc will assist Sea to quantify SPM-0404 levels in Clinical Phase 1 and Ph.1b Trials*

CAMBRIDGE, MA / ACCESS Newswire / April 6, 2025 / Sea Pharmaceuticals, LLC (Sea) today announced its selection of Inotiv Inc. (NASDAQ:NOTV) for pre-clinical development IND-enabling studies to support the advancement of Sea's lead molecule SPM-0404 as a potential new oral medicine to treat tinnitus, epilepsy and S-ALS. Sea's SPM-0404 and a second-generation molecule SPM-0606 represent a portfolio strategy of discovery and development of potent, selective, CNS-penetrant molecules targeting excitatory glutamate neurotransmission. A 100% Sea-owned patent estate protects Sea's novel chemical composition of matter in separate filings.

J.P. Pearson PhD, CEO and Founder of Sea Pharmaceuticals LLC said: "Sea is thrilled to work with Inotiv Inc., a company that has contributed to the development of many safe and effective medicines approved worldwide including development work of hundreds of IND molecules."

Dr. John E. Sagartz DVM, PhD, Inotiv's Chief Strategy Officer and scientific collaborator with Dr. Pearson for over 20 years offered further comments: "Inotiv is excited to work with Sea to help advance their small molecule therapeutics toward the treatment of significant CNS diseases for which there are currently unmet medical interventions. Given Inotiv's success working on many types of synthetic chemical therapeutics and biotherapeutics, we are well positioned to assist Sea in development strategy, to perform IND-enabling studies, and to conduct investigative studies."

Sea's molecules act as selective dual AMPAR (AMPA receptor), KAINR (kainate receptor) antagonists (DAKAs). DAKAs dampen the activity of the excitatory neurotransmitter glutamate which plays an important role in many physiological, neurological and neurobehavioral functions. Accordingly, AMPAR and KAINR represent two important glutamate-gated ion channel (GGIC) targets to treat CNS pathologies. Both are clinically validated drug targets for epilepsy, and both are clinically promising drug targets for tinnitus. AMPAR is a clinically promising drug target for S-ALS.

Dr Pearson said: "Sea's novel oral DAKA molecules are designed not only to address constant bothersome tinnitus but also epilepsy and sporadic ALS with the potential for improved clinical efficacy and clinical tolerability versus prior DAKAs."

Tinnitus patients and S-ALS patients urgently need effective and safe medicines. And a continued need exists for more effective and better tolerated therapeutic options for epilepsy.

- Tinnitus ranges from negligible to impactful (bothersome), which may be accompanied with impaired sleep, concentration, and/or relationships, as well as severe depression and/or anxiety.
- There are documented extreme cases of tinnitus leading to suicide.
- USA Tinnitus patient estimates: i) 7.8 M (million) moderate to severe CBT; ii) 8 M intermittent bothersome tinnitus; iii) 0.7 M catastrophic tinnitus; iv) >16 M non-bothersome tinnitus.
- Epileptic seizures can result in accidents and/or death. There are 3.5 M epilepsy patients in the USA and 30% still have seizures refractory to FDA-approved treatments.

- ALS is a fatal adult neurodegenerative disease of motor neurons, which is inherited in 10% of patients (familial ALS) and is non-inherited in the remaining 90% of patients (S-ALS).

- ALS is diagnosed with an incidence of 1.6 per 100,000 person years. 50% of patients survive years after diagnosis (10% survive 10 years). ALS patients have high morbidity leading to death.

- Two FDA-approved drugs for S-ALS slow its progression by months but do not prevent death.

Sea's pre-clinical investigational drugs offer the potential to provide breakthrough treatments for tinnitus, epilepsy and ALS patients.

About

Sea Pharmaceuticals LLC (Sea) is a private pre-clinical stage therapeutics research-and-development (RCD) company founded twelve years ago by J.P. Pearson and E. J. Martinez in March 2013. Sea is operated in Cambridge, Massachusetts USA. The Company invents, discovers, synthesizes, and develops novel synthetic biologically active neurotherapeutic molecules as potential oral medicines for patients with certain types of high-medical need CNS (central nervous system) disorders. Sea is advancing Sea's own proprietary molecules that are potent and selective dual AMPAR, KAINR antagonists. Sea's lead molecule SPM-0404 is in IND-enabling studies as a potential oral treatment for tinnitus, epilepsy, and ALS. Biological testing is conducted by Sea using pharmacologically evoked currents recorded by whole cell patch-clamp *in vitro* electrophysiological studies of intact native rat brain slice neurons and transfected human HEK293 cells expressing human recombinant GGIC subunits. SPM-0404 shows potent and selective *in vitro* biological activity (bioactivity) as a dual action antagonist of either AMPAR currents or KAINR currents in whole cell patch-clamp electrophysiology recordings [using either rat neurons or human recombinant cells]. SPM-0404 treatment in rodents shows potent and robust anti-seizure *in vivo* efficacy in the mouse 6-Hz psychomotor seizure model and the rat maximal electroshock seizure (MES) model. SPM-0404 is well tolerated *in vivo* in rodents with an acceptable therapeutic window. Single oral administration of SPM-0404 *in vivo* penetrates into the CNS of rats and non-human primates (NHPs) with acceptable CNS pharmacokinetics (PK in cerebrospinal fluid, CSF) and systemic whole-body plasma PK in both species. Multiple oral administration of SPM-0404 *in vivo* once-daily for 5-days is well tolerated in rats with acceptable PK (both systemic and CSF SPM-0404 levels). More at https://www.seapharmaceuticals.com

Tinnitus is a persistent neurological disorder of the brain and auditory pathway and involves the perception of sound during silence. Tinnitus can be constant or intermittent and can manifest as various sounds (e.g. ringing, hisses, buzzing, screeching, beeping, clicking, chirps, tones or other sounds). It may be impactful (bothersome) or benign, impairing sleep, concentration, or relationships (refs 1-3). It can be accompanied by neuropsychiatric symptoms of severe depression and/or anxiety. There are documented extreme cases of tinnitus leading to suicide. Tinnitus can result from repeated loud sound exposure (e.g. music, noise), or auditory injury (e.g. gunfire, bomb- blast, high-intensity noise), TBI (traumatic brain injury), age-related hearing loss, CNS infection, or idiopathic. Tinnitus neuro-pathophysiology likely involves two GGICs, AMPAR and KAINR. A global prevalence estimate of chronic tinnitus is 9.8% (this is one in every ten people), and severe tinnitus affects 2.3% (or one in every fifty people) of the world's population (ref. 4). Global incidence is 1,164 per 100,000 person years. Clinical scales exist for measuring tinnitus impairment in patients including the THI (tinnitus handicap inventory) and other clinical scales, (Refs. 5-7). No therapeutic molecules are FDA-approved to treat tinnitus. An *in vivo* animal model of single traumatic loud noise induced tinnitus exists (refs. 8-10). More at https://www.ata.org

Refs 1. Bauer CA 2018. New England Journal Medicine (NEJM) 378:1224; 2. Tyler RS, Baker LJ 1983 J. Speech Hearing Disorders (JSHD) 48:150; 3. Tyler R et al 2008. Am. J Audiol. 17: S176; 4. Jarach C et al (Langguth B) 2022. JAMA Neurology 79:888; 5. Newman CW et al 1996. Arch. Otolaryngology Head Neck Surgery (AOHNS) 122:143; 6. Newman CW et al 1998. Journal American Academy Audiology (JAAA) 9:153; 7. Zeman F et al. (Langguth B) 2011. Otolaryngology Head Neck Surgery (OHNS) 145:282; 8. Bauer CA (Brozoski TJ) et al. 2001. J Assoc Res. Otolaryngology (JARO) 2:54; 9. Brozoski TJ (Bauer CA) et al 2007. JARO 8:105; 10. Bauer CA (Brozoski TJ) et al 2013. PLoS One 8: e64726.

Epilepsy is a neurological brain disorder characterized by recurrent seizure episodes (ref. 1). Seizures involve excessive electrical discharges in brain neurons that may induce involuntary body movements (convulsions) and/or disturbances in consciousness, cognitive function, attention (awareness), sensation (vision, hearing, taste), bowel function, or bladder function. Epilepsy may result in falls, lethal accidents, depression, or suicide. Epilepsy can be caused by traumatic brain injury, stroke, tumor, infection, or may be idiopathic (unknown origin). Epilepsy patho-physiology involves targets in the brain which may include ion channels, neurotransmitter transporters and neuro-transmitter catabolic enzymes (ref. 2). The ion channel drug targets may include sodium, calcium, ligand gated ion channels e.g. gamma-aminobutyric acid $GABA_A$ (chloride permeable channels, potassium, or glutamate gated ion channels (AMPAR, KAINR) (refs. 2-3). Epilepsy affects

3.5 M in the USA, and 30% are refractory to current anti-seizure drugs (ref. 4).
More on Epilepsy at https://www.ninds.nih.gov/health-information/disorders/epilepsy-and-seizures

Refs 1. Scheffer IE et al. (French J). 2017. Epilepsia 589:512 (clinical classification); 2. Rogawski MA. 2002. p. 3-22. *In* Book Levy R et al. (Editors) "Antiepileptic Drugs." 5th Edition. Lippincott Williams C Wilkins. Philadelphia; 3. Sills GJ, Rogawski MA. 2020. Neuropharmacology. 168:107966; 4. Chen Z et al. (Kwan P). 2018 JAMA Neurology 75:279; 5. Barton ME et al (White HS). 2001. Epi. Res 47:217 (methods *in vivo* pharmacology models to study anti-seizure efficacy and therapeutic window in rodents: 6-Hz psychomotor seizure model, MES maximal electroshock seizure model).

Amyotrophic Lateral Sclerosis (ALS) is a lethal neurodegenerative motor neuron (MN) disease of high morbidity, causing progressive loss of muscle control. Death occurs by respiratory failure. Currently there are 30,000 ALS patients in USA (ref.1). Outcomes: 50% mortality in 2.5 years after diagnosis (90% mortality in 10 years). The vast majority (90% of all ALS cases) are non-inherited and are called sporadic ALS (S-ALS). The other 10% of ALS cases are inherited and are called familial ALS (F-ALS). 1% of all ALS patients have inherited SOD1 mutation. ALS age of onset: 58 - 63 years for S-ALS and 47 - 52 years for F-ALS. Symptoms of ALS onset: Limb-onset found in 2/3 cases: weakness in arms or legs. Bulbar-onset 1/3 cases: difficulty speaking or swallowing.

More on ALS at https://www.ninds.nih.gov/health-information/disorders/amyotrophic-lateral- sclerosis-als

Clinical molecular pathophysiology of spinal MNs from post-mortem human S-ALS patients suggests aberrantly active dysfunctional AMPARs as a target in S-ALS (ref. 2-5). Pre-clinical *in vivo* studies in genetically modified mice conditionally expressing abnormal AMPARs in MNs support AMPARs as a therapeutic target in S-ALS (refs. 6-10).

References (refs) 1. Feldman EL, et al. 2022. Lancet 400:1363 (clinical ALS review); 2-10 [Kwak S C Seeburg PH] 2. Kawahara Y et al. 2004 Nature 427:801; 3. Hideyama T et al 2012 Neurobiol Dis. 45:1121; 4. Aizawa H et al 2010 Acta Neuropath 120:75; 5. Hideyama T, Kwak S. 2011. Fr. Mol. Neurosci (S-ALS neuro-pathophysiology review). 4:1; 6. Yamashita T, et al. 2017 Genes 8: 60 (S-ALS review); 7. Higuchi M, et al 2000 Nature 406:78; 8. Hideyama T, et al. 2010 J. Neurosci. 30:11917; 9. Yamashita T, et al 2013 EMBO Mol Med 5:1710; 10. Akamatsu M, et al 2016 Sci Reports 6:28649.

Forward-Looking Statements (FLS) and Disclosures. This press release contains "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1955 that are based on the current expectations and beliefs of Sea. All statements, other than statements of historical fact, are statements that could be deemed FLS, including any statements on the outcome, benefits and synergies of collaborations, or potential collaborations, with any other company. Pharmaceutical development is a high-risk business, and the majority of IND molecules fail to become approved medicines. FLS involve significant risks and uncertainties, including those discussed in this press release. You should not rely on any FLS. Drs. Pearson, Martinez, Sagartz, Brozoski, Langguth and Kwak own stock in Sea.

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