On Thursday November 11, 2024 at 11:00AM ET

Sea Pharmaceuticals Advancing Oral Neurotherapeutics as Potential Medicines for Tinnitus, Epilepsy, and ALS in Collaboration with TCG GreenChem

- ***Sea's novel synthetic molecules act at the neurotransmitter glutamate pathway on two clinically validated targets in the central nervous system, "the CNS"***
    - ***Two potent, selective, pre-clinical stage molecules are being advanced as possible treatments for three therapeutic indications***
- ***Sea's lead SPM-0404 in investigational new drug-enabling studies for tinnitus, epilepsy, and ALS***
    - ***TCG GreenChem will conduct CMC (Chemistry, Manufacturing, & Controls) development on SPM-0404***

CAMBRIDGE, MA / ACCESSWIRE / November 14, 2024 / Sea Pharmaceuticals, LLC (Sea) today announced the advancement of two orally-administered neurotherapeutic molecules as potential new medicines for high need neurological disorders. Sea's lead molecule SPM-0404 and a second-generation molecule SPM-0606 are part of a portfolio strategy of discovery and development of novel, potent, selective oral compounds targeting the glutamate pathway.

Glutamate is a neurotransmitter in the CNS found in the majority of brain synapses: the specialized contacts where neurons (nerve cells) communicate. Glutamate's action as a neuron-to-neuron signaling molecule is essential for many physiological, neurological and neurobehavioral functions. Some neurotherapeutic investigational new drugs (INDs) or FDA-approved drugs that modulate glutamate neurotransmission have shown therapeutic potential in CNS maladies such as epilepsy and other seizure disorders, bothersome tinnitus, the lethal neurodegenerative disease ALS, some neuro-developmental disorders (including Rett syndrome and autism spectrum) and certain neuro-psychiatric disorders (e.g. anxiety-related disorders or OCD obsessive-compulsive).

Sea's molecules SPM-0404 and SPM-0606 are biologically active as dual AMPAR, KAINR antagonists (also called "DAKAs"). Sea's DAKAs act on two well-studied glutamate pathway targets, AMPAR and KAINR, glutamate gated-ion channels (GGICs) found on neurons in the CNS. These two GGICs are clinically validated in epilepsy and are clinically promising human drug targets of constant bothersome tinnitus (CBT) as well as intermittent bothersome tinnitus (IBT). AMPAR is a clinically promising human drug target in sporadic ALS (S-ALS).

SPM-0404 is in IND-enabling studies as a potential oral treatment for three indications (1) CBT, (2) epilepsy, and (3) S-ALS. Single oral administration of SPM-0404 *in vivo* penetrates into the CNS of rats and non-human primates with acceptable CNS pharmacokinetics (PK) and systemic whole-body PK in both species. A 100% Sea-owned patent estate on DAKAs including the above two compounds protects Sea's novel chemical composition of matter in separate filings.

J.P. Pearson PhD, Founder, CEO & CSO of Sea said: "The two neurotherapeutic drug targets AMPAR and KAINR have promising therapeutic potential in several CNS disorders (both in neurology and in neuropsychiatry) beyond their clinical validation in epilepsy. Sea's novel oral DAKA molecules are designed not only to address epilepsy but at least two other unserved neuro-therapeutic indications tinnitus and S-ALS with the potential for improved clinical efficacy and clinical tolerability versus prior DAKAs."

Patients with tinnitus, epilepsy, or S-ALS, are unserved or underserved.

- Tinnitus can be either impactful (bothersome) or negligible. Impactful tinnitus may impair sleep, concentration, and/or relationships; and can be accompanied by severe depression and/or anxiety. There are documented extreme cases of tinnitus leading to suicide. There are no FDA approved medicines for treating tinnitus. Tyler RS et al 1983 and 2008 characterized subtypes of patients suffering impactful tinnitus [CBT, IBT, or catastrophic tinnitus (Cat. T)] versus negligible tinnitus. Based on global tinnitus data (Jarach C et al. 2022) in the USA an estimated >7 million (M) patients suffer moderate to severe CBT; an estimated 8 M suffer IBT; and 0.7 M suffer Cat. T.
- Epileptic seizures can result in accidents and/or death. There are 3.5 M epilepsy patients in USA and 30% still have seizures on current treatments.
- ALS is a fatal adult neurological disease, which is inherited in 10% of ALS patients (familial ALS) but non-inherited in the remaining 90% of ALS patients (S-ALS). ALS is diagnosed with an incidence of 1.6 per 100,000 people and prevalence is 4.4 per 100,000 people (Feldman et al 2022). 50% of patients survive 2.5 years after diagnosis (10% survive 10 years).

Sea also announced today a strategic collaboration with TCG GreenChem, Inc. of Ewing NJ USA (TCG GC) who will conduct chemical development for Sea on lead molecule SPM-0404 producing the cGMP material (current good manufacturing practices) for IND-enabling studies and for Clinical Trials. Chris H. Senanayake PhD (TCG GC Founder, CEO & CSO) and Joe D. Armstrong III PhD (chief business officer) are synthetic organic chemists who have made >500 IND molecules and several FDA-approved drugs in their combined >65 years in the pharma industry.

Dr. Pearson said: "Sea has built a strong working collaboration with Drs. Senanayake and Armstrong at TCG GC to enable process optimization and analytical method development to ensure the highest quality pharmaceutical manufacturing of SPM-0404 in a cost-effective manner. Chris and Joe have an impressive record of drug making. Their notable synthetic organic chemistry skills led Sea to choose TCG GC to synthesize SPM-0404 for IND-enabling studies & clinical trials."

Dr. Senanayake said: "TCG GC looks forward to CMC development (Chemistry, Manufacturing and Controls) of Sea's molecule SPM-0404 to advance it forward. TCG GC provided Sea with a chemical developmental feasibility plan for the cGMP manufacture of SPM-0404. TCG GC will supply SPM-0404 for IND-enabling tox studies, for Clinical Phase 1 (drug safety study), and for Ph1b trials. We are delighted to be a strategic partner with Sea Pharma."

About

Sea Pharmaceuticals LLC (Sea) is a private pre-clinical stage therapeutics research-and-development (R&D) company founded by J.P. Pearson and E. J. Martinez in 2013 and operated in Cambridge, Massachusetts USA. The Company invents, discovers, 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. More at https://www.seapharmaceuticals.com

TCG GreenChem, Inc. is the US subsidiary of TCG Lifesciences Pvt. Ltd., a leading global contract research and manufacturing services (CRAMS) company in the area of drug discovery, development and commercialization. TCG GC offers seamless CMC development services including synthetic organic process chemistry, process research, and cGMP active pharmaceutical ingredient (API) development & delivery. TCG GC is based in Ewing, New Jersey (NJ) USA where it employs >55 PhDs synthetic organic chemists, analytical chemists, project managers, and support. TCG GC has state of the art cGMP facilities both in Ewing NJ USA and in Hyderabad India. More at https://tcggreenchem.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, buzzing, beeping, clicking, chirps, screeches, hisses, tones). It may be impactful (bothersome) or benign, affecting 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% and severe tinnitus affects 2.3% 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 (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

References

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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

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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).

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Forward-Looking Statements (FLS) and Disclosures. This press release contains FLS that are based on the current expectations and beliefs of Sea (and in some instances of TCG GreenChem Inc). 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. Development of pharmaceuticals is 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 and more fully described to investors or funders of Sea. Sea has filed Form D at USA Securities and Exchange Commission (SEC). Drs. Pearson, Martinez, Senanayake, Armstrong, Langguth, Brozoski and Kwak each own stock in Sea.

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