Chronos Therapeutics Announces Positive Pre-clinical Proof of Concept in MS Fatigue Model.

Patents for the Fatigue programme awarded in USA and Europe.

Oxford, UK 4 December 2018: Chronos Therapeutics Ltd (Chronos) the private biotech company focused on behavioural and degenerative diseases of the brain, announced today that its small molecule, CT-005404 demonstrated positive pre-clinical results in an *in vivo* model of fatigue in multiple sclerosis (MS). Chronos also announced the grant of composition of matter patents covering the programme in the USA and Europe.

Up to 80% of MS patients suffer from moderate to severe fatigue regardless of disease subtype (relapsing-remitting versus progressive forms). This significantly impacts their quality of life. There are currently no drugs specifically approved for patients with MS who suffer from fatigue and even off label treatments used offer sub-optimal efficacy with a burden of side effects.

CT-005404, a new chemical entity is a highly selective atypical dopamine transporter (DAT) inhibitor. The programme represents a novel approach to the treatment of fatigue in MS. Chronos also announced strengthening of its IP position with the grant of two US patents and one European patent covering lead and back up molecules (US Patent No. 9,908,897 and US Patent No. 9,920,053, European Patent No. EP 3194385).

Dr Fraser Murray, CSO, said: *"Atypical DAT inhibitors represent an exciting therapeutic opportunity that is highly differentiated, having a non-stimulant profile, addressing perceived issues with abuse liability. Selectively inhibiting DAT is a novel approach in the treatment of fatigue in MS, a significant area of unmet medical need. We believe that the clear efficacy of CT-005404 seen in a pre-clinical model of fatigue in MS, with very high selectivity vs other monoamine transporters gives us confidence to advance CT-005404 towards clinical development. Given the conserved mechanism of central fatigue across multiple diseases this also presents an opportunity to treat patients with fatigue across a range of diseases"*

Dr Huw Jones, CEO added: *We have generated yet another set of clear proof of concept data showing promise in a drastically under-served area of brain medicine. Again* we have achieved this speedily and with financial efficiency showing that we have the ability to re-start acquired programmes, improve on them and move them efficiently to significant development milestones. I applaud our senior team for these achievements. We now have three programmes in radically different brain diseases all at a similar stage of development that have promise in alleviating significant suffering."*

* See Chronos press release 2 May announcing Binge Eating Disorder programme POC.

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Notes to Editors

About Chronos Therapeutics

Chronos Therapeutics Ltd is a privately held Oxford, UK-based biotechnology company focused on diseases of ageing, brain and nervous system disorders. Chronos has a dedicated laboratory in Oxford which screens for activity of drugs in brain disease through its proprietary platform, Chronoscreen™.

The company has an extensive library of re-purposed molecules showing promise for brain and neurological diseases. The lead compound, RDC5, is being developed for the fatal neurodegenerative disease, Amyotrophic Lateral Sclerosis (ALS). A phase 1 study is complete for RDC5 and the company anticipates completing Investigational New Drug (IND) activities in 2019 in anticipation of starting a Phase 2a clinical study in ALS patients.

Chronos recently acquired three new chemical entity (NCE) development programmes for CNS diseases. The most advanced programme is initially targeting fatigue associated with multiple sclerosis. The company's orexin-1 antagonist programme is following closely behind and expected to enter the clinic at a similar time. Other, earlier programmes address serious behavioural and neurodegenerative conditions.

Chronos' major shareholders include Vulpes Life Sciences, Odey Asset Management, the University of Oxford, an affiliate of Shire PLC, the Board and Management. For additional information, please visit: www.chronostherapeutics.com

About Multiple Sclerosis and Fatigue

An estimated 2.3 million people globally have multiple sclerosis (MS) according to the Multiple Sclerosis International Federation. Fatigue is the most common symptom of the disease. It occurs in 75% to 95% of patients with MS and as many as 40% of patients have described it as the single most disabling symptom of the disease.

There are two major types of fatigue in MS. These two types of fatigue are probably separate problems related to the MS. The first type is a general feeling of tiredness. It may feel as if one has not slept the night before. This feeling may be worse in the afternoons or after activity. People may feel that they are unable to do as many tasks without getting tired as they did before. A second type of fatigue is muscular. In this type, there is increased weakness after repeated activity. Often, this occurs with walking. People may find that they are dragging one leg or are more unsteady.

About Addictive Behaviours

There are a number of addictive behaviours that represent significant unmet medical needs and require novel treatments. Chronos is targeting binge eating, alcohol and nicotine addictions.

Binge eating is an eating disorder where a person feels compelled to overeat on a regular basis through regular "binges" or consumption of very large quantities of food over a very short period of time, even when they are not hungry. The condition tends to first develop in young adults, although many people do not seek help until they are in their 30s or 40s. There is a 1 in 30 to 1 in 50 chance of a person developing binge eating disorder at some point during their life and it can lead to a variety of health problems that can, in extreme circumstances, be life-threatening. Whilst more women suffer from the condition than men, binge eating is not particularly uncommon in men with the prevalence ratio of approximately 1.5 women for every man with the disorder.

Nicotine and alcohol addiction: Addiction involves repeated use of a psychoactive substance (such as nicotine or alcohol) causing a user to be intoxicated with a compulsion to take the preferred substance and often a determination to obtain the substance by almost any means. Addicts also have difficulty in modifying or stopping substance use. They build up tolerance to the addictive substance, sometimes requiring more and more for the same effect and develop withdrawal syndromes when use is interrupted.

Addiction to nicotine via tobacco kills one person prematurely every six seconds and 50% of long term smokers according to World Health Organisation (WHO) reports, with tobacco attributed deaths predicted to rise to 8 million globally a year by 2030. The US Centers for Disease Control and Prevention (CDC) also notes that about 480,000 Americans die every year from smoking-related causes involving cancers (chiefly lung cancer), stroke, heart disease and chronic obstructive pulmonary disease (COPD).

Excessive alcohol use (as caused by addiction or binging) has caused 10% of deaths among working-age adults aged 20-64 years in the USA with economic costs in 2010 in the USA alone of $249 billion. The WHO also estimates that harmful alcohol use causes 3.3 million deaths a year, globally. Short-term health risks, most often the result of binge-drinking, include accidents, injuries, alcohol poisoning and risky sexual behaviours. Over a longer time excessive alcohol use can lead to chronic diseases including high blood pressure, cancers, mental health and social problems.

About Amyotrophic Lateral Sclerosis (ALS)

The motor neurone disease Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's Disease) is a fatal neurodegenerative disease characterised by progressive death of the primary motor neurones in the central nervous system. Symptoms include muscle weakness and muscle wasting, difficulty in swallowing and undertaking everyday tasks. As the disease progresses,

the muscles responsible for breathing can fail, gradually causing dyspnoea or difficulty in breathing.

ALS has an average prevalence of 2 per 100,000. Prevalence is higher in the UK and USA than in many other countries, up to 5 per 100,000. There are estimated to be over 50,000 patients in the USA and 5,000 patients in the UK with the condition. Mortality rates for ALS sufferers are high with 10-year survival after diagnosis below 10% and average survival of 39 months from diagnosis. There is only one drug currently approved for treatment in the EU and as of 2017, two drugs approved for the condition in the USA.

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