e-therapeutics

e-therapeutics plc
("e-therapeutics" or the "Company")

COVID-19 Project Update

Oxford, UK, 8 December 2020 – e-therapeutics plc (AIM: ETX) announces the results of experimental testing on the compounds for the treatment of COVID-19 identified using its proprietary Network-driven Drug Discovery (NDD) platform.

In March 2020, the Company announced its intention to deploy its network biology platform to identify clinical stage compounds that either singly or in combination could be repurposed rapidly to treat COVID-19. We chose to approach this by focussing on therapeutic strategies that target host systems, thereby minimising the risk of resistance and potentially being effective for the treatment of other viral infections.

From our previous work using network models of SIRS (Systemic inflammatory response syndrome) seen in indications such as sepsis, we had identified a class of small molecule compounds, a mechanism and target that was able to silence the 'cytokine storm' generated in human blood cells by a range of inflammatory triggers. In March 2020, we undertook an *in silico* analysis of data sets from human cells infected with SARS-CoV-2 and generated network models of the cellular machinery that the virus had 'hijacked'. Analysis of both our SIRS work and the SARS-CoV-2 networks revealed a key common process which was simultaneously important to the virus and the hyperinflammatory response. Our platform predicted that inhibition of the same target, GRP94, that was effective in suppressing hyperinflammation would also be effective in disrupting the virus's ability to replicate.

In May 2020, small molecule compounds predicted by our platform were tested in validated SARS-CoV-2 *in vitro* assays at WuXi AppTech. These compounds showed potent anti-inflammatory and anti-viral activity. We report here that *in vitro* assays have confirmed our *in silico* predictions and we have identified a clear mechanism, target and clinical stage compounds. These compounds are active against GRP94 and have anti-inflammatory and anti-viral activity against Sars-CoV-2. This activity generalises to other alpha and beta coronaviruses and is expected to be generically applicable, raising the prospect of utility against both existing coronaviruses that cause serious disease such as SARS and MERS and against new emergent strains of coronavirus.

The clinical stage compounds identified have been developed in humans for alternative indications and have an established safety profile in man. These, and other selective compounds sharing this target, could be rapidly deployed into clinical trials to treat patients with serious Covid-19 disease. Given our mechanistic insights, it would also be feasible to develop novel, highly selective drugs against GRP94. We continue to work on repurposable combinations using our platform and have compound combinations currently in testing. We anticipate data that will enhance our understanding further in Q1 2021.

Chairman & CEO Ali Mortazavi said:

" e-therapeutics' platform has the ability to start with any biological process of relevance to disease and to identify compounds and targets that can modulate that process in a therapeutic setting. This data set is a strong validation of our platform and the network biology approach to drug discovery. e-Therapeutics' computational biology platform is capable of discovering new chemical matter, novel drug targets and uncovering new mechanisms. Here, we have deployed that capability to investigate known compounds in a novel context. We have uncovered new mechanisms that

mitigate infection-induced hyperinflammation as well discovering a potent anti-viral strategy. Our findings have highlighted Bardoxolone Methyl which is already the subject of an investigator led COVID-19 trial (NCT04494646).

The surprise finding of this compound's anti-viral activity alongside its well observed anti-inflammatory properties has led us to file a patent (GB2017631.9) which describes the use of Bardoxolone and related compounds to treat Covid-19 and other viral diseases. Previous knowledge of similar compounds has focused on the activation of the NRF2 pathway. Here, we show that both the anti-viral and anti-inflammatory properties we have observed depend on GRP94. We demonstrate that other selective GRP94 inhibitors may also be active anti-virals against a range of coronaviruses. Should Bardoxolone Methyl be progressed from its Phase 2 safety evaluation in NCT04494646 into Phase 3, we would be happy to share our anti-viral analysis with the sponsor.

To date, no compounds with this type of potent dual activity have been reported and clinical approaches have focused on combination drug therapies using anti-inflammatory compounds such as dexamethasone combined with anti-virals such as Remdesivir. Irrespective of our findings for Bardoxolone, we believe that our project will open deeper interest in selective GRP94 inhibitors and GRP94 as a possible target for future development of therapeutics not only for COVID induced hyper-inflammation/infection but potentially other viral infections. A presentation can be found on our website at : https://www.etherapeutics.co.uk/wp-content/uploads/2020/12/COVID-Project-Update-05122020.pdf The company intends to publish this work in a highly regarded scientific journal in the coming months."

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About e-therapeutics plc

e-therapeutics plc is an Oxford, UK-based company with a powerful computer-based approach to drug discovery, founded on its industry-leading expertise in network biology to fully capture disease complexity. The Company combines network science, machine learning, artificial intelligence, statistics and access to big data with expertise in drug discovery and development to transform the search for new medicines and intervention strategies.

e-therapeutics has developed an *in silico* laboratory that enables the rapid screening of millions of compounds and the identification of small sub-sets that are enriched for highly active hits. Its proprietary platform also has novel applications in functional genomics, being able to analyse complex genetic datasets, provide a deep understanding of pathological mechanisms and distil actionable insights for the discovery of novel drugs, biomarkers and diagnostics.

e-therapeutics has deployed and validated its disease-agnostic drug discovery platform both in house and with partners, including Novo Nordisk, Galapagos NV and a US-based, top 5 pharmaceutical company.