



C4X Discovery Holdings plc

("C4XD", "C4X Discovery" or the "Company")

Business Update

Key discovery programmes make positive progress

1 October 2019 – C4X Discovery Holdings plc (AIM: C4XD), a pioneering Drug Discovery company, today announces progress across a number of key programmes in line with its strategy.

Dr Clive Dix, Chief Executive Officer of C4XD, said: *"Momentum continues to build within the C4XD portfolio. Recent exciting new industry sickle cell disease data supports the potential of our NRF-2 activator programme as an alternative treatment for poorly served patients. This new data supplements learnings from our early discussions and increases our confidence towards a sickle-cell disease focused out-licensing.*

"In order to maximise the value for our shareholders, we have focused on rapidly advancing the next wave of potential revenue-generating assets, whilst maintaining our considered approach to the deployment of available funds. In particular, we plan to progress the lead target from our collaboration with Horizon Discovery into a C4XD-led commercial Drug Discovery programme.

"We are excited that the world class Drug Discovery being carried out by the team at C4XD has built a highly valuable portfolio of new medicines that will allow us to strike further lucrative deals with pharma partners as demonstrated by Indivior's grant awarded by NIH HEAL to initiate phase 1 clinical studies of our Orexin 1 programme for the treatment of opioid use disorder. We are very confident about delivering these deals in the near future and beyond."

Business Update

The Company continues to progress its strategy to deliver Drug Discovery programmes for out-licensing (NRF-2 activator, IL-17 inhibitor and LifeArc collaboration) and early stage multi-target disease area opportunities for novel targets identified from its proprietary technology and collaborations (Horizon Discovery Group ("Horizon") and Taxonomy3[®] derived Parkinson's Disease projects).

Highlighted Drug Discovery Programmes

Oral NRF-2 Activator Programme

C4XD is progressing a series of novel potent activators of the NRF-2 pathway for the treatment of inflammatory diseases. In C4XD studies, multiple lead compounds show > 12hr duration of action following low oral dosing on activation of NRF-2 in key tissues such as lung and liver as well as blood. Pre-candidate nomination studies are currently underway with candidate selection anticipated for Q1 2020.

Partnering discussions to date have confirmed commercial interest for NRF-2 in Sickle Cell Disease (SCD). NRF-2 activators are shown to directly increase foetal haemoglobin and reduce oxidative stress and inflammation, with significant potential for the treatment of haemolysis-related complications in SCD. The Board believes that upcoming C4XD data will be valuable in driving a competitive out-licensing process focused on SCD.

Oral IL-17 Inhibitor Programme

C4XD has identified small molecules that can selectively block IL-17 activity whilst keeping molecular size of the molecule in the traditional "drug-like" range. In C4XD studies, optimisation of lead oral compounds



continues to achieve effective drug concentration in the blood. Based on recent industry disclosures¹ this level of drug concentration is predicted to be efficacious in pre-clinical inflammatory models. C4XD continues to receive strong interest from potential partners for this high value target, particularly driven by the C4XD series profiles.

LifeArc Oncology and Inflammation Collaboration

The initial phase of the collaboration with LifeArc has been successful. In initial studies, multiple hit compounds have progressed with the aim of generating a lead series with *in vivo* activity for oncology and inflammatory indications by Q2 2020. Significant industry activity from multiple pharmaceutical companies for the target of interest at recent scientific meetings supports the ongoing partnering potential of this programme.

Oral Orexin-1 Receptor Antagonist Programme

In March 2018, Indivior entered a license agreement to obtain exclusive global rights to develop and commercialize C4X3256, C4XD's oral Orexin-1 Receptor Antagonist programme for the treatment of opioid use disorder. On 27 September 2019, Indivior was awarded a National Institutes of Health (NIH) grant to advance C4X3256 from preclinical status through Phase 1 clinical evaluation and perform the necessary toxicology and drug metabolism studies to enable Phase 2 studies.

Early Stage Multi-Target Disease Area Opportunities

Horizon Oncology Collaboration

C4XD and Horizon entered into an exclusive target discovery partnership in December 2018 to take forward high-value novel synthetic lethal² oncology targets discovered through in-depth CRISPR-Cas9 analyses conducted by Horizon, which have the potential to offer an alternative route to creating new oncology drugs. The collaboration has made rapid progress and has now generated comprehensive *in vitro* validation data packages for the lead novel target in the collaboration.

In vitro studies have confirmed that inhibition of this target induces cell death that is dependent on the presence of cancer-specific mutations, thereby demonstrating synthetic lethality. Additional *in vivo* studies have shown that knock out of the gene inhibits growth of implanted colon cancer cells with a KRAS mutant background. As an enzyme, the target is expected to be highly amenable to targeting with small molecules and is nearing progression into C4XD-led Drug Discovery programmes, with additional targets to follow the development pathway.

Taxonomy3[®]-derived Parkinson's Disease projects

C4XD continues to progress the validation of its proprietary Taxonomy3[®]-derived novel targets for Parkinson's Disease, utilising a diversified strategic approach:

- (i) C4XD's internally led biological validation studies are near completion for targets with existing tool compounds. This provides a low risk starting point from which to rapidly initiate Drug Discovery programmes for promising targets with some known chemistry and biology.
- (ii) The Phoremest collaboration initiated in June 2019 uses Phoremest's SITESEEKER[®] platform to generate biological validation for all Taxonomy3[®] targets as well as providing chemical starting points for highly novel Taxonomy[®] targets without existing chemistry in the literature. This enables the progression of more challenging, but high potential targets.
- (iii) The e-therapeutics collaboration has identified additional novel biological pathways derived from Taxonomy3[®]'s novel genes which are currently being evaluated to identify additional targets with the potential to start new Drug Discovery programmes.



Notes:

1. *Direct inhibition of IL-17A with small molecule compounds identified from DEL. Thomas Franch, Ph.D Chief Scientific Officer Nuevolution A/S, Oxford Global 5th Drug Discovery USA Congress, 11th October, 2018, San Diego. Global Discovery to Development Innovation Forum 2019, 14-15th May 2019, Amsterdam. Thorsten Thormann, Vice President Research Leo Pharma.*
2. *The term “synthetic lethality” was originally coined by geneticists in the 1940s to describe the process where mutations in two different genes together resulted in cell death but independently did not affect viability. In cancer, targeting inhibition of the critical DNA repair pathway has the potential to cause tumour cells with specific mutations (e.g. KRAS and p53) to self-destruct.*

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Notes to Editors:

About C4X Discovery

C4X Discovery (C4XD) aims to create the world’s most productive Drug Discovery engine by using cutting-edge technologies and expertise to efficiently deliver best-in-class small-molecule medicines to clinical partners for the benefit of patients. The Company’s business model focuses on replenishing big pharma discovery pipelines and driving returns through revenue generating pre-clinical licensing deals. In 2018, C4XD successfully out-licensed a pre-clinical programme in addictive disorders to Indivior in a deal worth up to \$294m.

C4XD has a state-of-the-art suite of proprietary technologies across the Drug Discovery process and accesses further innovative capabilities and expertise through its growing network of partners. The Company is actively advancing its diverse pre-clinical discovery portfolio which is focused on inflammation, neurodegeneration and oncology (including immuno-oncology). Opportunities to maximise value from the portfolio are proactively driven by C4XD’s commercial division. The Company is led by a highly experienced management team and Board who have delivered significant value creation within the healthcare sector.

For additional information please go to: www.c4xdiscovery.com