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Data demonstrating PDE3/4 inhibitor RPL554 enhances CTFR-dependent currents in cystic fibrosis airway epithelia

Poster presented at North American Cystic Fibrosis Conference, USA

8 October 2015, Cardiff – Verona Pharma plc (AIM: VRP.L), the drug development company focused on first-in-class medicines to treat respiratory diseases, announces that a poster will be presented later today at the North American Cystic Fibrosis Conference in Phoenix, Arizona, USA, 8- 10 October 2015.

Poster number 231, entitled: “The Dual Phosphodiesterase 3 and 4 Inhibitor, RPL554, Enhances Forskolin-Stimulated, CTFR-Dependent Currents in Cystic Fibrosis Airway Epithelia” investigated the effect of RPL554, an inhaled dual PDE3/4 inhibitor, on the Cystic Fibrosis Transmembrane conductance Regulator (CFTR), an anion channel that is mutated in Cystic Fibrosis (CF).

In a preclinical model, RPL554 was shown to have CFTR-stimulatory properties and that CFTR activation by RPL554 is mediated by its inhibition of PDE4 in cells from CF patients with the R117H/F508del mutation. The data reported suggest that CFTR activation may contribute to the action of inhaled RPL554 in chronic obstructive pulmonary disease (COPD) and asthma, and further support the concept that RPL554 may be an attractive novel therapeutic option for the treatment of CF, an orphan disease with about 70,000 people afflicted worldwide. This work was partly funded through the Venture and Innovation Award which Verona Pharma received from the UK CF Trust in November 2014. This poster also extends the work presented at the 2014 North American Cystic Fibrosis Conference in Atlanta, Georgia, USA, announced in a press release on 29 September 2014.

Verona Pharma's lead drug, RPL554, is a first-in-class drug currently in Phase II trials as a nebulised treatment for acute exacerbations of COPD in the hospital setting.

The full abstract for this poster is reproduced below.

THE DUAL PHOSPHODIESTERASE 3 AND 4 INHIBITOR, RPL554 ENHANCES FORSKOLIN- STIMULATED, CFTR-DEPENDENT CURRENTS IN CYSTIC FIBROSIS AIRWAY EPITHELIA
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Efficient spatial and temporal regulation of cAMP is required for cell signal transduction by protein kinase A (PKA) and the exchange protein directly activated by cyclic AMP (EPAC). The enzymes responsible for degrading cAMP are the cyclic nucleotide phosphodiesterases (PDEs), of which at least 11 different isoforms have been identified in humans. The Cystic Fibrosis Transmembrane conductance Regulator (CFTR) is the PKA-activated anion channel that is mutated in Cystic Fibrosis (CF). Inhibitors of both PDE3 and PDE4 have been shown to elevate intracellular cAMP and activate CFTR in various airway epithelial models, suggesting they could serve as potential therapeutic targets for CF. Using qPCR, of the 7 PDEs surveyed, we found PDE4D to be the most highly expressed isoform in CFBE-WT and CFBE-F508del cells, contributing ~64% of the total PDE expression in both cell lines (n=3). Relatively high levels of PDE7A (11.1 ± 2.6% of the total in WT cells and 7.5 ± 0.7% in ΔF-508 cells; n=4; $p>0.05$) and PDE8A (27.2 ± 4.7% in WT cells and 18.1 ± 1.2% in F508del cells; n=3; $p<0.01$) were also observed, suggesting they may also contribute to CFTR regulation. RPL554, a dual PDE3/4 inhibitor in Ph2a clinical trials, is a "first-in-class" inhaled treatment for respiratory diseases and has been shown to have significant bronchodilator and anti-inflammatory (including anti- neutrophilic) activity in humans (Franciosi, L.G., et al., Lancet Respir Med, 2013. 1(9) 714-727). RPL554 caused a dose-dependent increase in CFTR-dependent short circuit current (Isc) across CFBE-WT cells, with 10μM RPL554 eliciting 65.9 ± 4.5% (n=3) of the maximal forskolin response. Similar results were also obtained with primary WT human bronchial epithelial cells. To

determine if the RPL554 stimulation was mediated by inhibition of PDE3 or PDE4 in primary human bronchial epithelial cells (HBEs), and whether PDE inhibition was able to activate CFTR in CF airway epithelia, the specific PDE inhibitors Milrinone (PDE3) and Rolipram (PDE4) were tested on HBEs from three R117H/F508del CF patients. Forskolin (2μM) increased Isc by 1.43 ± 0.11μA cm-2 (n=16), which was enhanced to 2.06 ± 0.19μA cm-2 in cells that had been pre-treated with Lumacaftor for 24 h ($p<0.01$; n=15) demonstrating Lumacaftor was able to act as a corrector in these cells. The acute addition of Rolipram, RPL554, and Rolipram + Milrinone (without Lumacaftor pre-treatment) increased forskolin- stimulated Isc by 0.92 ± 0.17μA cm-2 ($p<0.01$; n=5), 0.92 ± 0.19μA cm-2 ($p<0.05$; n=8) and 0.64 ± 0.14μA cm-2 ($p<0.05$; n=9), respectively. No increase was induced by Milrinone alone (Isc increased by -0.03 ± 0.10μA cm-2; n=5). The similar magnitude of the response caused by Rolipram and RPL554, together with the absence of an effect of Milrinone, suggests that the CFTR activation by RPL554 is mediated by inhibition of PDE4. These data suggest that CFTR activation may contribute to the action of inhaled RPL554 in COPD and asthma and further support the concept that RPL554 may be an attractive novel therapeutic option for the treatment of CF.

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About Verona Pharma plc
Verona Pharma is a clinical-stage biopharmaceutical company focused on developing and commercializing innovative therapeutics for the treatment of respiratory diseases with significant unmet medical needs. Verona Pharma's product candidate, RPL554, is a first-in-class, inhaled, dual inhibitor of the enzymes phosphodiesterase 3 and 4 that acts as both a bronchodilator and an anti-inflammatory agent in a single compound. In clinical trials, treatment with RPL554 has been observed to result in statistically significant improvements in lung function as compared to placebo and has shown clinically meaningful and statistically significant improvements in lung function when added to two commonly used bronchodilators as compared to either bronchodilator administered as a single agent. RPL554 has also shown anti-inflammatory effects and been well tolerated in clinical trials. Verona Pharma is developing RPL554 for the treatment of chronic obstructive pulmonary

disease (COPD), cystic fibrosis, and potentially asthma.

Forward Looking Statements
This press release contains forward-looking statements. All statements contained in this press release that do not relate to matters of historical fact should be considered forward-looking statements.

These forward-looking statements are based on management's current expectations. These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from our expectations expressed or implied by the forward-looking statements, including, but not limited to, the development of DPI and MDI formulations of RPL554 and the potential for these formulations to increase the market opportunity for the product, if approved.

These and other important factors could cause actual results to differ materially from those indicated by the forward-looking statements made in this press release. Any such forward-looking statements represent management's estimates as of the date of this press release. While we may elect to update such forward-looking statements at some point in the future, we disclaim any obligation to do so, even if subsequent events cause our views to change. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date of this press release.
