ASX ANNOUNCEMENT **23 August 2017**

Positive Data from Cynata MSCs in Second Preclinical Asthma Study

- Clear efficacy data for Cynata's proprietary Cymerus™ MSCs in second preclinical study in a clinically-relevant model of asthma
- Cymerus MSCs caused significantly greater reduction of airway hyperresponsiveness compared to corticosteroid treatment
- Data suggest Cymerus MSCs can be administered alone or in combination with corticosteroids to treat the airway hyperresponsiveness associated with asthma
- Completion of this study will further advance the path towards clinical trials

Melbourne, Australia; 23 August 2017: Australian stem cell and regenerative medicine company, Cynata Therapeutics Limited (ASX: CYP), is pleased to announce further highly promising data supporting the efficacy of its proprietary Cymerus™ mesenchymal stem cells (MSCs) in a second preclinical asthma study.

The study was conducted under the supervision of Associate Professor Samuel and Dr Simon Royce of the *Monash Lung Biology Network*,[1] focusing on the effects of Cymerus™ MSCs in combination with or in comparison to the corticosteroid dexamethasone, which is commonly used to treat exacerbations of asthma in human patients. The study used a well-established mouse model of chronic allergic airways disease that closely resembles asthma in humans. This part of the study focused on airway hyperresponsiveness (AHR), which is a key clinical manifestation of asthma.

Initial results from this study have demonstrated that, as expected, treatment with dexamethasone alone significantly improved AHR compared to untreated controls ($p<0.05$). However, treatment with either Cymerus™ MSCs alone, or Cymerus™ MSCs in combination with dexamethasone, resulted in a substantially greater suppression of AHR, which was significantly superior to that seen with dexamethasone treatment alone ($p<0.01$). All treatments were administered by the intranasal (IN) route.

These exciting results lead on from a previously-reported study (announced 2 March 2017), which found that both intravenous (IV) and IN administration of Cymerus™ MSCs caused statistically significant improvements in the three main features (airway hyperresponsiveness, inflammation and airway remodelling) of asthma in this model. Furthermore, IN delivery of Cymerus™ MSCs completely reversed pathologic collagen deposition (a sign of airway remodelling/fibrosis).[2] Of note, studies by the same group have found that other types of stem cells did not have similar effects to IN Cymerus™ MSCs in this model, unless used in combination with other drugs.

"It is very striking that Cymerus™ MSCs, whether alone or in combination with dexamethasone, had a significantly greater effect on decreasing AHR in this model than dexamethasone alone. We are now conducting further analyses on the effects of these cells on other features of the disease process including inflammation and airway remodelling," said Associate Professor Samuel.

"These findings raise the possibility that Cymerus™ MSCs may have superior efficacy to corticosteroids in some asthma patients, in addition to offering a way to treat this condition without the side-effects and/or resistance associated with steroid therapy," said Dr Kilian Kelly, Cynata's Vice President, Product Development. "Furthermore, it was important to show that Cymerus™ MSCs can be administered in combination with corticosteroids, especially in the context of initial clinical trials, in which most patients are likely to be undergoing corticosteroid treatment at the time of enrolment."

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Cynata Therapeutics Limited
Level 3, 62 Lygon Street, Carlton, Victoria 3053, Australia
PO Box 7165, Hawthorn North, Victoria 3122
T: + 613 9824 5254 **F:** + 613 9822 7735 **E:** admin@cynata.com
ABN - 98 104 037 372

CONTACTS: Dr Ross Macdonald, CEO, 0412 119343, ross.macdonald@cynata.com
Rosa Smith, Australia Media Contact, 0475 305 047, rosa.smith@mcpartners.com.au
Laura Bagby, U.S. Media Contact, 312-448-8098, lbagby@6degreespr.com

About Cynata Therapeutics (ASX: CYP)

Cynata Therapeutics Limited (ASX: CYP) is an Australian clinical-stage stem cell and regenerative medicine company developing therapies based on its proprietary Cymerus™ stem cell technology platform. Cymerus overcomes critical issues in the production of therapeutic mesenchymal stem cells (MSCs) by enabling the economical manufacture of commercial-scale MSCs, independent of multi-donor limitations. Cymerus' novel approach utilises induced pluripotent stem cells (iPSCs) derived from a single blood donation to generate mesenchymoangioblasts (MCAs), a precursor that is used to manufacture an unlimited number of therapeutic MSCs. Cynata's unique "off-the-shelf" Cymerus platform has the potential to create a new standard in the development and manufacture of stem cell therapeutics.

About the Preclinical Study in the Ovalbumin-Induced Allergic Airways Disease Model

Female wild-type BALB/c mice at 7–8 weeks of age were maintained under specific pathogen-free conditions, under a fixed lighting schedule with access to food and water *ad libitum*. A well-established ovalbumin-induced chronic allergic airways disease model was used as previously described.[3] Briefly, mice were sensitised with intraperitoneal injections of ovalbumin and alum on days 1 and 14, and then challenged with a nebulised aerosol solution of ovalbumin for 30 minutes, three times a week for 8 weeks (from days 21 to 77). The study involved a total of 40 mice, which were randomly assigned to one of the following five groups (eight animals per group):

1. Untreated controls (no asthma)
2. Untreated sensitised animals (asthma)
3. Sensitised animals (asthma), treated with IN infusion of MSCs
4. Sensitised animals (asthma), treated with IN infusion of DEX
5. Sensitised animals (asthma), treated with IN infusion of MSCs + DEX

All MSC-treated animals received a dose of 1 million cells by the specified route of administration on two occasions (once weekly from weeks 9-11). DEX (0.5mg/ml) was administered once daily from weeks 9-11. The following endpoints were then measured at week 11 (after 2-weeks of MSC ± DEX treatment):

i) Inflammation score – as a measure of airway inflammation (AI)
ii) Goblet cell metaplasia – as a measure of AI-induced airway remodelling (AWR)
iii) Epithelial thickness – as a measure of AWR
iv) Sub-epithelial collagen thickness – as a measure of AWR/fibrosis
v) Total lung collagen concentration – as a measure of AWR/fibrosis
vi) Epithelial TGF-β1 staining – as a measure of AWR
vii) Subepithelial myofibroblast density – as a measure of AWR
viii) Gelatinase (MMP-2 and MMP-9) expression/activity – as a measure of AWR
ix) AHR/reactivity in response to the bronchoconstrictor methacholine, measured by invasive plethysmography (a measure of lung function).

[1] The Monash Lung Biology Network is a consortium, which includes researchers from the Biomedicine Discovery Institute and Department of Pharmacology at Monash University, Melbourne.

[2] Royce SG, Rele S, Broughton BRS, Kelly K, Samuel CS. Intranasal administration of mesenchymoangioblast-derived mesenchymal stem cells abrogates airway fibrosis and airway hyperresponsiveness associated with chronic allergic airways disease. FASEB J. 2017 Jun 16. pii: fj.201700178R.

[3] Temelkovski J et al. An improved murine model of asthma: selective airway inflammation, epithelial lesions and increased methacholine responsiveness following chronic exposure to aerosolised allergen. Thorax. 1998;53(10):849-56.