ASX ANNOUNCEMENT **11 December 2017**

Final Preclinical Asthma Study Confirms Efficacy

- Clear confirmation of efficacy of Cynata's proprietary Cymerus™ MSCs in second preclinical asthma study
- Treatment with Cymerus MSCs in clinically-relevant model caused significantly greater reduction of airway hyperresponsiveness, airway remodelling and fibrosis compared to corticosteroid treatment
- Combination therapy involving Cymerus MSCs and corticosteroids resulted in a pronounced synergistic effect, producing marked anti-inflammatory effects in addition to the benefits seen with Cymerus MSC treatment alone
- Strong efficacy data from this trial advances path towards clinical trials in asthma, a disease that impacts +300 million people globally[1]

Melbourne, Australia; 11 December 2017: Australian stem cell and regenerative medicine company, Cynata Therapeutics Limited (ASX: CYP), is pleased to announce that it has received the final report on the effects of Cymerus MSCs in combination with or in comparison to the corticosteroid dexamethasone in a further preclinical asthma study. Corticosteroids are considered to be the most effective medications for controlling asthma (when taken regularly).

The study was conducted under the supervision of Associate Professor Chrishan Samuel and Dr Simon Royce of the *Monash Lung Biology Network*,[2] using a well-established mouse model of chronic allergic airways disease, which closely resembles asthma in humans, and includes several key features: airway inflammation; airway remodelling/fibrosis (structural changes in the airways due to excess fibrous tissue); and airway hyperresponsiveness.

Daily administration of dexamethasone (a corticosteroid), demonstrated marked anti-inflammatory effects in this model. It reduced airway inflammation by approximately 55% and airway inflammation-induced goblet cell metaplasia (abnormal changes in the cells responsible for producing mucus) by approximately 80% (both $p<0.001$ vs untreated mice). However, dexamethasone displayed weak anti-remodelling and anti-fibrotic effects, and only reduced airway hyperresponsiveness by approximately 30% over the 2 week-treatment period.

In comparison, once-weekly administration of one million Cymerus MSCs resulted in striking reductions of airway remodelling, fibrosis and airway hyperresponsiveness. Most notably, subepithelial collagen deposition (a measure of fibrosis) and airway TGF-β1 expression levels (a measure of airway remodelling) were normalised to levels equivalent to mice in which asthma had not been induced, while airway hyperresponsiveness was reduced by 70-75% (all $p<0.001$ vs untreated mice).

When the two treatments were combined, a pronounced synergistic effect was achieved, resulting in similar anti-inflammatory effects to dexamethasone alone and similar reductions in remodelling, fibrosis and airway hyperresponsiveness to Cymerus MSCs alone.

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

Summary of Results

	Dexamethasone alone	Cymerus MSCs alone	Combination
Airway inflammation	↓↓	↓	↓↓
Goblet cell metaplasia	↓↓	-	↓↓
Airway remodelling	↓	↓↓↓	↓↓↓
Fibrosis	↓	↓↓↓	↓↓↓
Airway hyperresponsiveness	↓	↓↓	↓↓

Key: The ↓ symbol represents a reduction of the relevant feature, and the number of arrows represents the relative extent of reduction. Each feature listed is a negative manifestation in the asthma model, so in all cases a decrease is a positive outcome.

"The combination of Cymerus MSCs and dexamethasone resulted in maximal improvement for each endpoint measured. Hence, it can be concluded that such a combination therapy has the potential to improve treatment outcomes in asthmatic patients," said Associate Professor Samuel.

Dr Kilian Kelly, Cynata's Vice President, Product Development commented: "These findings further strengthen the body of evidence supporting the use of Cymerus MSCs as a potential asthma treatment. In addition to confirming that Cymerus MSCs had a greater effect than corticosteroid treatment on several key manifestations of asthma in this model, these results provide clear evidence that Cymerus MSCs can work in synergy with corticosteroids. Overall, the results suggest that Cymerus MSCs could be used as a standalone treatment, for example in patients who are unable to tolerate corticosteroids, or as an add-on therapy in patients who are unable to gain control of their condition with existing medications".

Ends

CONTACTS: Dr Ross Macdonald, CEO, Cynata Therapeutics: Tel: +61 (0)412 119343; email ross.macdonald@cynata.com
Daniel Paproth, Australia Media Contact, +61 (0)421 858 982 , daniel.paproth@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 that is developing a therapeutic stem cell platform technology, Cymerus™, originating from the University of Wisconsin-Madison, a world leader in stem cell research. The proprietary Cymerus™ technology addresses a critical shortcoming in existing methods of production of mesenchymal stem cells (MSCs) for therapeutic use, which is the ability to achieve economic manufacture at commercial scale. Cymerus™ utilises induced pluripotent stem cells (iPSCs) to produce a particular type of MSC precursor, called a mesenchymoangioblast (MCA). The Cymerus™ platform provides a source of MSCs that is independent of donor limitations and provides an "off-the-shelf" stem cell platform for therapeutic product use, with a pharmaceutical product business model and economies of scale. This has the potential to create a new standard in the emergent arena of stem cell therapeutics and provides both a unique differentiator and an important competitive position.

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 Global Asthma Report - 2014

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

[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.