Unlocking Stem Cell Therapy Potential

Cynata is a clinical-stage biotech company developing stem cell therapy products using its proprietary Cymerus™ platform technology for mesenchymal stem cell (MSC) manufacture. The Cymerus™ platform uses stem cells derived from a single donation of whole blood from a single donor as source material rather than relying on tissue donations (eg bone marrow, adipose tissue) from multiple donors. This technology could pave the way for Cynata to exploit the potential of stem cells in developing therapeutic products to treat serious disorders.

Novel and scalable approach for consistent results

The benefits of Cynata's approach include: (1) consistency: Cynata's MSC finished products are consistent, robust and reproducible; and (2) scalability: the process is extremely scalable and avoids the problems of inter-donor variability found with conventional methods. This process could lead to a more standardised and 'pharmaceutical-grade' MSC product.

440-patient Phase 3 trial in osteoarthritis underway

The Australian Phase 3 SCUlpTOR trial of intra-articular CYP-004 injected the drug into the knee of patients with mild to moderate knee osteoarthritis (OA) represents the largest such study conducted using MSCs and the most rigorous investigation of stem cell therapy for musculoskeletal conditions to date. A positive readout could provide the scientific evidence of efficacy that redefines therapeutic approaches in OA.

Safety + efficacy results supported GvHD Phase 2 …

Lead candidate CYP-001 met all clinical endpoints and demonstrated positive safety and efficacy data for the treatment of steroid-resistant acute graft-versus-host disease in a Phase 1 trial. This was a major milestone for establishing safety and supports starting trials for all other indications at Phase 2.

…. and attracted a major strategic partner in Fujifilm

Fujifilm has been a licence partner since 2019 for the use of CYP-001 for aGvHD after entering a licensing agreement for an upfront fee of US$3m. As per the agreement, Fujifilm will assume all future development costs following the positive Phase 1 data. Cynata can earn up to US$43m as well as royalties of ~10% on future sales. Cynata's robust pre-clinical package in multiple therapeutic targets, together with the current clinical pipeline, has the potential to attract further corporate partners.

CYP-001 enters open-label Phase 2 study for respiratory failure

A recently commenced 24-patient open label Phase 1/2 trial of intravenously administered CYP-001 in adults admitted to an intensive care unit with respiratory failure, including acute respiratory distress syndrome, could render preliminary efficacy signals. Given the COVID-19 pandemic, any positive trend could re-rate the stock.

Valuation: $2.95 per share on risk-adjusted NPV

We value Cynata Therapeutics at A$408m or A$2.95 per share on an undiluted basis, using a risk-adjusted net present value (rNPV) method to discount future cash flows through to 2034, consistent with the expiry of current patent families.

Cynata Therapeutics Limited is a clinical-stage stem cell and regenerative medicine company. It is leveraging its proprietary therapeutic stem cell platform technology, Cymerus™, originally based on discoveries made at the University of Wisconsin–Madison (UWM), a global centre of excellence in stem cell research, to develop allogeneic (off the shelf) induced pluripotent stem cell (iPSC)-derived MSC therapeutic products.

Stock	CYP
Price	A$0.57
Market cap	A$82m
Valuation	A$2.95 per share

Company data	
Net cash	A$28.2m (March 2021)
Shares on issue	138.6m

Clinical pipeline, June 2021

- CYP-001: intravenous infusion (GvHD, resp failure)
- CYP-002: intramuscular injection (CLI)
- CYP-004: intra-articular injection (knee OA)

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Investment Thesis: Next-Generation Stem Cell Production Platform

Company Profile: Reliable and Consistent MSC Manufacturing at Commercial Scale

Cynata Therapeutics Limited is an Australian stem cell and regenerative medicine company. Cynata is leveraging its therapeutic stem cell production platform technology, Cymerus™, to develop therapeutic mesenchymal stem cell (MSC) products using discoveries made at the University of Wisconsin–Madison (UWM) and licenced to Cynata. The company was established in 2011 and listed on the ASX in 2013.

Cynata's Cymerus™ technology leverages a novel manufacturing process based on a major technological stem cell breakthrough. The technology uses human-induced pluripotent stem cells (iPSCs) derived from whole blood, rather than conventional tissue sources, to manufacture MSCs under Good Manufacturing Practice (GMP) standards. This process eliminates the major issues hampering conventional MSC production: supply, scalability, potency and consistency. This affords Cynata a substantial competitive advantage over conventional methods of MSC manufacture.

Clinical trial history: successful Phase 1 results on safety and efficacy signals

Cynata's first human study using iPSC-derived MSCs was a 16-patient Phase I clinical trial evaluating lead candidate CYP-001 in steroid-resistant acute graft-versus-host disease (GvHD). This trial rendered positive safety and efficacy data, culminating in a licensing agreement with Fujifilm in 2019. The successful completion of the Phase I trial in GvHD allowed Cynata to advance clinical development of its iPSC-derived MSCs across multiple indications.

Clinical pipeline: exploration across multiple indications

High-priority clinical programs include:

- **osteoarthritis, Phase 3:** the 440-patient, NHMRC-funded Phase 3 SCUlpTOR (stem cells as a symptom and structure-modifying treatment for medial tibiofemoral osteoarthritis) trial of CYP-004, Cynata's MSC product candidate for treatment of osteoarthritis
- **respiratory failure (COVID and other causes), Phase 2:** a 24-patient Phase 2 trial assessing the efficacy of CYP-001 in patients admitted to intensive care with respiratory distress, including acute respiratory distress syndrome (ARDS). This trial has received ethics committee approval and has been expanded to include causes beyond COVID-19 such as influenza. Patient enrolment commenced with the first subject in May 2021.

Potential Near-Term Catalysts

- CYP-001 – Phase 2 trial in respiratory distress
- CYP-001 – Phase 2 trial in aGvHD
- CYP-004 – Phase 3 trial in knee osteoarthritis
- CYP-002 – Restarting trials in critical limb ischemia
- TBD (MSC-seeded silicon dressing) – Phase 1/2 in diabetic foot ulcers

Valuation $2.95 on Risk-Adjusted NPV

We value Cynata Therapeutics at A$408m or A$2.95 per share on an undiluted basis, using a risk-adjusted net present value (rNPV) method to discount future cash flows through to 2034, consistent with the expiry of current patent families.

Sensitivities and Risks

Cynata Therapeutics is subject to all the risks typically associated with biotech company drug development, including the possibility of unfavourable outcomes in clinical trials, regulatory decisions, success of competitors, financing, and commercial decisions by partners or potential partners, including timing.

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Company Outlook: Cynata Removes Major Roadblock to MSC Potential

Cynata currently is developing several products (see Exhibit 1), targeted at a range of indications and delivered in a number of ways. All of these products are manufactured using the Cymerus™ platform, which has removed the major obstacles to scalable manufacture of a consistent MSC product and opened the possibility for major advances in therapeutic treatments using stem cells. Positive preclinical results to date and Cynata's range of research collaborations have resulted in a diversified pipeline of clinical programs.

Exhibit 1 – Cynata's clinical pipeline

Product	Indications	Dose (delivery)	Status	Next milestone	Notes
CYP - 001	acute Graft vs host disease/ organ transplantation	Intravenous	Phase 2 planning	Bypass Phase 2 - Excellent phase 1 results facilitate Cynata progressing directly to phase 2/3 clinical trials in multiple other indications	Phase 1 results published in prestigious journal, Nature Medicine. Overall response = 87%, Survival rate ≥ 87%. US$2m payment on Phase 2 completion.
CYP - 001	Respiratory failure (inc ARDS)	Intravenous	24 pt Phase 2 underway (open for enrolment).	First patient enrolled 24/05/2021. Beginning Q3FY22 headline results from study should be available.	Trial is currently open for enrolment. Cynata to execute strategy to accelerate recruitment.
CYP - 002	Critical limb ischaemia	Intramuscular	Phase 2 ready	Currently on hold	Encouraging efficacy signals in preclinical study.
CYP - 004	Knee Osteoarthritis	Intra-articular	440pt Phase 3 underway - funded by a NHMRC grant	11 Nov - Patient enrolment opened and trial commenced, seeking 440 patients.	Funded by a NHMRC grant (no cash contribution from Cynata) and sponsored by University of Sydney.
TBD	Diabetic foot ulcers	MSC-seeded silicon dressing	Phase 1/2 planning	Cynata expects trial to commence in 2HCY21	Worldwide exclusive licence agreement to Tekcyte's wound dressing technology for use in in diabetic foot ulcer clinical trial.

Source: Cynata Therapeutics.

Stem Cell Therapy: History, Science, and Clinical Utility in Modern Medicine

The history of stem cell therapy

Stem cells are undifferentiated (unspecialised) cells capable of developing into specific cells in the body as required. They are capable of self-renewal and multi-directional differentiation and can be found in both embryonic and adult organisms. Origins of the term 'stem cell' can be traced back to the 19th century when biologists used the label to describe the fertilised egg that becomes an organism, and the single-celled organism that acted as the ancestor cell to all living things in history.

The first therapy using stem cells was a bone marrow transplant performed in 1958. However, research into the potential of stem cells was reinvigorated in 1998 with the development of a method of culturing and growing human embryonic stem cells in the lab. In the decades since, clinical interest in stem cells and their potential as both regenerative medicine and drug development has surged.

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Types of stem cells – two broad groups

	Tissue-specific stem cells	Pluripotent stem cells
Alternative names	Adult stem cells Somatic stem cells	----
Sub-categories	• Mesenchymal stem cells, aka mesenchymal stromal cells (MSCs). *Note: Stem cell research and applications have been most advanced with MSCs to date due to clinical experience and their clinically useful properties.*	• Embryonic stem cells (ESCs) • Induced pluripotent stem cells (iPSCs). *Use of this type of stem cell is being opened up by Cynata's technology.*
Notable attributes	Multipotent: • Capable of self-renewal • Differentiation limited to tissue or organ where they are found	Pluripotent: • Can develop into an unlimited source of any cell type in the body • Can potentially form teratomas
Location in the body	Throughout the body in relatively low numbers	Pluripotent stem cells are developmentally immature and therefore found in the embryo. iPSCs are made in the lab

iPSCs technology[1] – reprogramming adult cells back to embryonic state

What are iPSCs? Cynata's Cymerus™ manufacturing technology leverages a technological discovery made in 2006 demonstrating it was possible to restore differentiated body cells back to the state of embryonic stem cells, to produce so-called **induced pluripotent stem cells** (iPSCs). iPSCs are generated from adult cells by reactivating a small number of genes using specific and defined factors, to transform the mature specialised cells back into an embryonic-like pluripotent state, a process called *reprogramming*.

What is special about iPSCs? iPSCs may be derived from nearly any cell in the body; typically cells from the skin or from blood are used. iPSCs are unique due to their embryonic-like properties, their ability to be cultured (grown in an artificial environment) indefinitely and be developed into almost any type of human cell. Notably, iPSC production does not involve the use of embryos and therefore avoids the ethical controversies associated with such use of embryos. While iPSCs are derived from a totally different source than embryonic stem cells (ESCs), both cell types have very similar properties, hence the enormous worldwide interest in their use in therapeutic applications.

What has held the technology back? Administering iPSCs on their own has no known therapeutic use: the utility comes from cells derived from iPSCs. Although cells derived from iPSCs have the benefits of ESCs without the ethical considerations, issues of premature cell death and safety concerns associated with abnormal cell growth (teratomas) and the risk of tumour formation (cancer) have challenged early iterations of the technology's production methods[2].

Focusing on mesenchymal stem cells (MSCs) – traditional sources and current shortcomings

The first major clinical investigation into the use of **mesenchymal stem cells** (MSCs) by biotechnology companies was in developing a treatment for acute graft-versus-host disease (aGvHD) using cells sourced from bone marrow tissue. MSCs have become one of the most important cell types under investigation in clinical trials for the development of cell therapies. MSCs have unique and valuable properties which are considered clinically attractive for therapeutic use. These include:

- their ability to regulate both immune and inflammatory responses through the secretion of cytokines, chemokines, growth factors and extracellular vesicles

[1] 2012 Nobel Prize in Physiology and Medicine awarded jointly to Shinya Yamanaka and John Gordon for discovering that mature cells can be reprogrammed to become pluripotent.

[2] Derivation of Induced Pluripotent Stem Cells by Lentiviral Transduction – Nethercott et al (2011)

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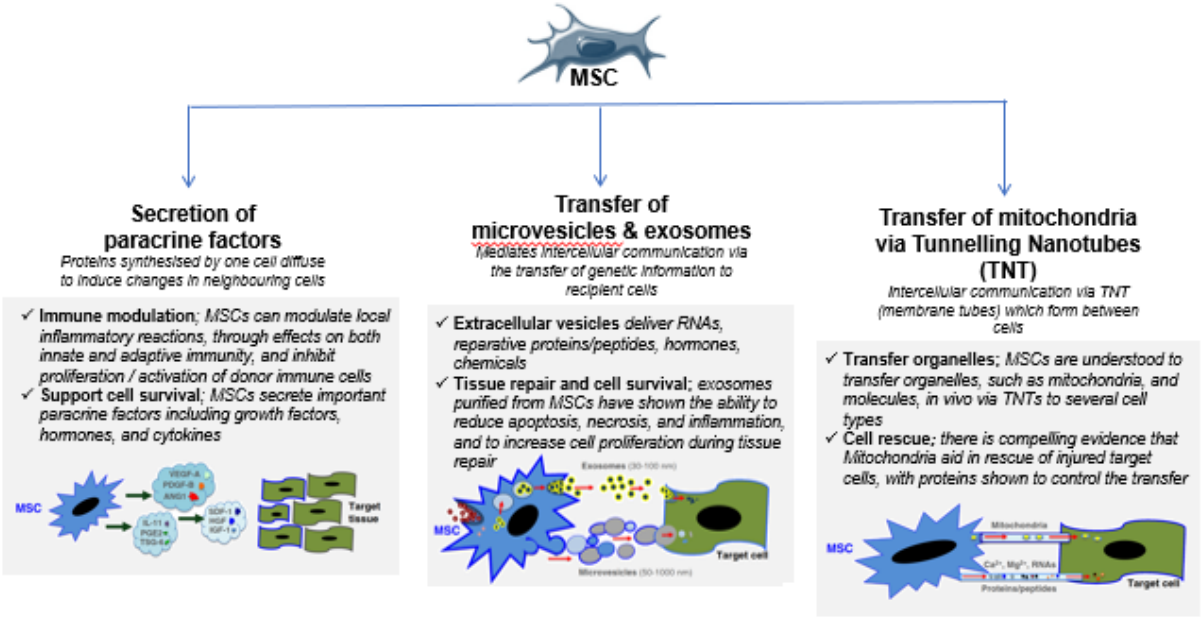
- the fact that they do not provoke an immune response, allowing them to be administered without donor-recipient matching
- their ability to adapt to microenvironments and secrete specific factors (cytokines and chemokines) in direct response to these adaptations.

Exhibit 2 – MSCs can regulate immune and inflammatory responses, making them attractive for therapeutic use



Source: Cynata Therapeutics.

MSCs are considered multipotent although with a more limited ability to differentiate compared to pluripotent stem cells. This means that under certain conditions, whether be it in vitro or in vivo, they can still mature and differentiate into multiple specialised cells.

Traditional sources of MSCs to date used in clinical trials have been bone marrow, adipose tissue, peripheral blood, cord blood and dental pulp. This has resulted in several shortcomings limiting production of MSCs and hampering their clinical development as therapeutics to date:

- the dependence upon an ongoing group of donors
- the variability between donors in terms of genetic differences
- the relative scarcity of MSCs in adult tissue
- the low proliferative capacity of adult stem cells compared to pluripotent stem cells, and subsequent loss of potency at high levels of expansion.

iPSC-derived MSCs address clinical and commercial shortcomings of current sources of MSCs

Cynata's proprietary stem cell technology, Cymerus™, represents a novel and innovative approach to manufacturing MSCs that addresses the shortcomings of conventional production processes whilst benefiting from their therapeutic potency. The Cymerus™ technology was developed based on research conducted at the University of Wisconsin–Madison (UWM), a leading centre of stem cell research globally, by Professor Igor Slukvin, a cofounder of Cynata. Cynata licensed the IP from WARF (University of Wisconsin). The Cymerus™ technology combines the ground-breaking technique of reprogramming differentiated human cells to iPSCs which are then differentiated with minimal expansion to mesenchymoangioblasts (MCAs), precursor cells for MSCs isolated at UWM. Production of MCAs as intermediates is a key aspect of Cynata's differentiated pathway approach to the manufacture of MSCs.

Using iPSCs originating from blood samples as a starting material addresses the current challenges of supply and consistency of MSCs. This technique exploits the effectively limitless capacity to expand iPSCs, thereby eliminating the need to rely on new donors and minimising the level of culture expansion at the level of MSCs.

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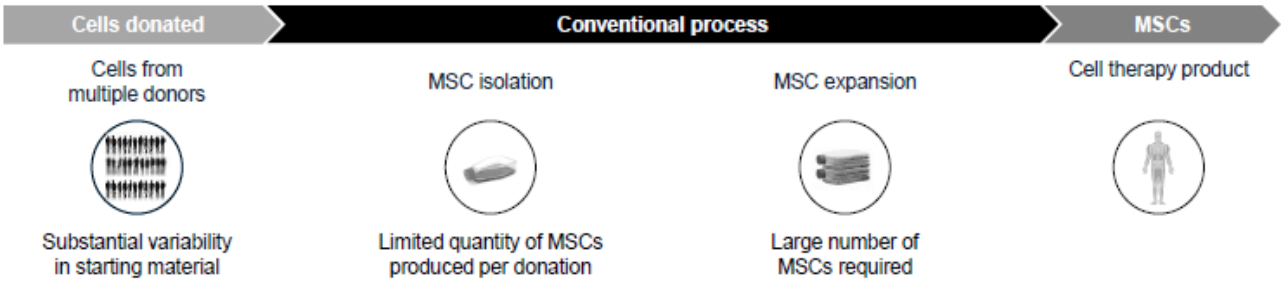
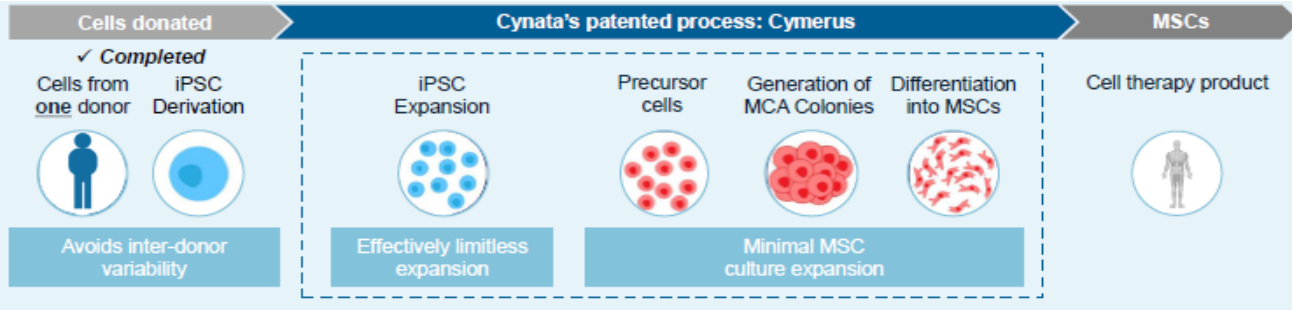
Exhibit 3 – Current conventional MSC manufacturing process



Source: Cynata Therapeutics.

Exhibit 4 – Cynata's Cymerus™ platform for MSC manufacture



Source: Cynata Therapeutics.

Cynata's Cymerus™ platform delivers a higher production capacity than achieved with other stem cell products. One vial of derived iPSCs (1 million cells) can produce 32,000 million MSCs. This allows for significant scale of production capabilities and consistency of batch, both important considerations in the commercial viability of stem cell products. Once produced, these cells are cryogenically preserved until required and can be stored for a minimum current validated shelf life of 2 years, although Cynata is working on extending this.

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Clinical Strategy – Validation Time Approaching for iPSC-derived MSCs

Due to their multifaceted mechanism of action and unique biological properties, MSCs have attracted significant interest and are being investigated across a broad range of clinical applications (see Competitive Landscape section later in report). Nonetheless, the shortcomings of current MSC manufacturing methods with respect to consistency and scalability have hampered clinical development generally and contributed, in our view, to the FDA's hesitancy to approve MSC-based therapies.

Cynata's innovative Cymerus™ technology addresses these issues and holds the promise of producing pharmaceutical-grade MSC products that can be manufactured at scale. This would represent an important competitive advantage for Cynata pending the success of current clinical trials.

Collaboration-Based Research Model Underpins Broad Pipeline and Multiple Opportunities

Since listing in 2013, the company's strategy for commercialising potential Cymerus™ therapeutic products has been to form development and commercialisation partnerships with leading academic and medical centres in Australia and overseas. This strategy has provided extensive preclinical testing of the Cymerus™ MSCs and yielded significant amounts of preclinical data across a range of indications, which should inform future clinical development programs and attract commercial partners.

Exhibit 5 – Cynata's broad preclinical pipeline provides multiple opportunities for Cymerus™ MSC products

Priority	Indications	Partners	Rationale	Notes
First order	Diabetic foot ulcers	CRC for Cell Therapy Manufacturing (Adelaide, SA)	Cymerus™ MSCs resulted in significantly faster wound healing than bone marrow-drived MSCs in preclinical model of diabetic wound.	Secured worldwide exclusive licence agreement to Tekcyte's wound dressing technology which will be utilised in Cynata's planned clinical trial in diabetic foot ulcers.
	Idiopathic pulmonary fibrosis	Monash University	Potent anti-inflammatory and anti-fibrotic effects of Cymerus™ MSCs in several different studies in pre-clinical models of allergic and fibrotic diseases of the lung.	New study by Prof. Samuel at Monash University in Melbourne to investigate in a pre-clinical model of lung disease the potential molecular mechanisms involved i the observed high potency of Cymerus™ MSCs.
	Renal transplantation	King Faisal Specialist Hospital and Research Centre, Riyadh, Kingdom of Saudi Arabia	Positive phase 1 data from CYP-001 Phase 1 study in steroid refractory-aGvHD.	Cited Phase 1 study of CYP-001 for the treatment of steroid-resistant acute graft versus host disease.
Second order	Asthma	Monash University	Proof of concept	Cymerus™ MSCs reduced airway hyper-responsiveness by 60-70% in animal mode of chronic allergic airways disease.
	Glioblastoma/Brain cancer	Harvard Medical School	Proof of concept	Cymerus™ MSCs found to express diagnostic and therapeutic anti-cancer agents and showed highly promising therapeutic benefits in different mouse tumour models.
	Heart attack	University of Sydney	Proof of concept	Cymerus™ MSCs enhance the recovery of the blood supply to the damaged heart.
	Coronary artery disease	UNSW	Proof of concept	Cymerus™ MSCs found to induce neovascularisation (growth of new blood vessels in an in vitro assay; Modification of the cell culture matrix (the material on which th cells are grown) was shown to "prime" Cymerus MSCs, and improve their ability to induce neovascularisation; The priming effects were maintained after the cells wer frozen and then thawed.
Future target areas	Fistula	N/A	N/A	
	Crohn's Disease	N/A	N/A	

Source: Cynata.

Cynata Advances into Phase 2 Trials with Several High-Value Indications

Cynata has investigated numerous disease areas and, having demonstrated the safety/tolerability of Cymerus™ MSCs with the Phase 1 trial of CYP-001 in GvHD, is now advancing into several mid- and late-stage trials. Exhibit 6 highlights the company's current clinical development pipeline and features the three most advanced clinical programs to date targeting:

- graft-versus-host disease (GvHD) (CYP-001)
- osteoarthritis (CYP-004)
- COVID-19–related respiratory failure (CYP-001)
- critical limb ischemia (CYP-002): Phase 2 ready (trial timing uncertain due to COVID-19)
- diabetic foot ulcers (DFU): Phase 1/2 planning underway.

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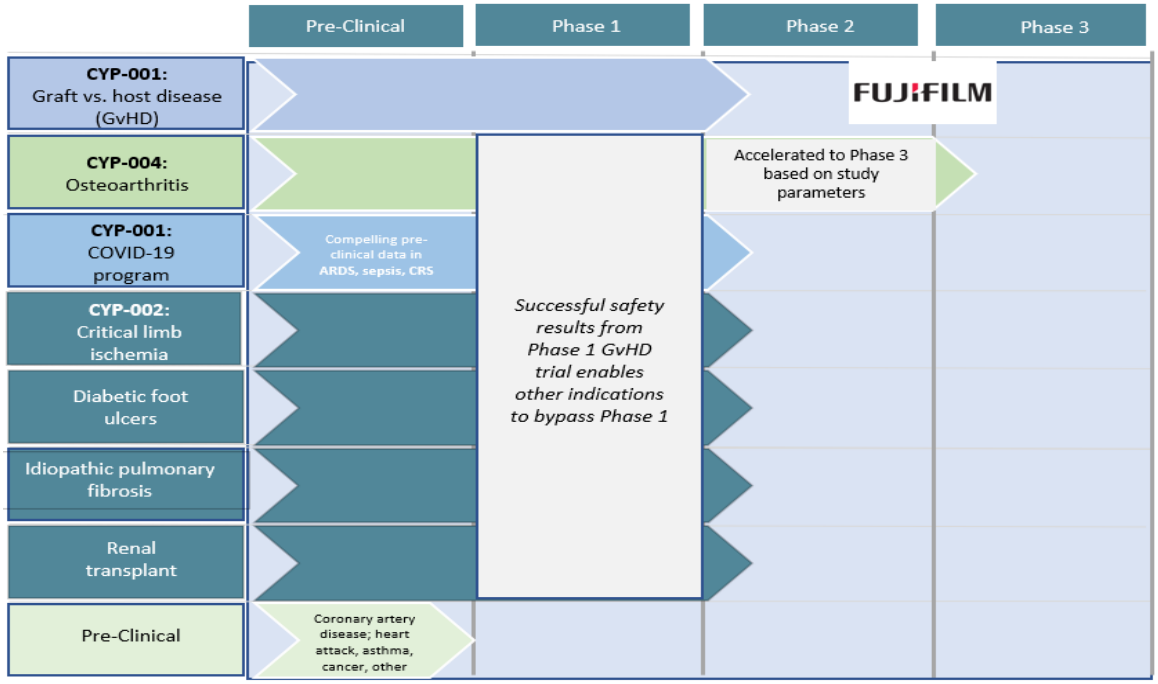
Exhibit 6 – Clinical development pipeline: advancing into several late-stage trials



Source: Cynata.

Graft versus Host Disease (CYP-001): First iPSC-MSC Trial

Disease overview and market opportunity

Graft versus host disease (GvHD) is a common and potentially life-threatening complication of allogeneic hematopoietic stem cell transplantation (HSCT, also called bone marrow transplants). GvHD occurs when the immune cells in the donor material (the graft) recognise and attack the recipient's tissues (the host) as foreign, causing inflammation and tissue damage. Bone marrow transplants are most often performed for cancer patients (particularly patients with multiple myeloma or leukaemia) after radiation or chemotherapy has damaged the immune system.

Corticosteroids are the first-line treatment for acute GvHD (aGvHD), although ~50% of these patients become refractory (resistant). There is currently no accepted standard-of-care treatment for steroid-resistant aGvHD. As such, the prognosis for these patients remains poor, with mortality rates in excess of 90%.

In 2019, approximately 20,000 allogeneic HSCTs were undertaken in Europe[3] and 9,500 in the US[4] (a total of about 30,000). Assuming 50% of HSCT recipients develop aGvHD, of which 50% will present as steroid refractory, we estimate the contestable market in 2019 was ~7,500.

Rationale – history of clinical development in aGvHD

MSCs act on most cells of the immune system and inhibit the proliferation, activation, and cytokine release of natural killer cells, and have therefore been viewed as promising treatments for aGvHD. Nonetheless and despite the launch of Mesoblast's Remestemcel-L, branded Temcell, in Japan by licensee partner JCR Pharmaceuticals in 2016, MSCs have yet to be approved by the FDA for any indication.

Cynata's preclinical data – positive findings in animal studies

Proof of concept was established in a mouse model of critical limb ischemia conducted in 2013. Preclinical results followed from animal studies of CYP-001 in a humanised mouse model of severe aGvHD showing that survival times

[3] Hematopoietic cell transplantation and cellular therapy survey of the EBMT-Passweg et al (2021).

[4] CIBMTR – Current uses and outcomes of HSCT 2020 (summary slides

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more than doubled compared with placebo (54 days versus 25.5 days). In this study, treated animals received either one or two doses of CYP-001, while control animals received only saline. A larger study of 60 animals completed in 2017 reaffirmed the safety profile of CYP-001 and rendered strong survival data along with substantial elucidation of mechanism of action.

Clinical – Phase 1 met all endpoints and supports advance to Phase 2 trials in multiple indications

The first in human trial of CYP-001 reported positive results from the 28-day, 100-day and two-year follow up of patients, meeting all clinical endpoints and supporting a move into Phase 2 trials across multiple indications. This was the first human clinical trial of an iPSC-derived MSC and was conducted in hospitals in the UK and Australia.

Subjects were screened and sequentially assigned to cohort A or cohort B (n = 8 per group). The subjects received intravenous infusions of CYP-001 on days 0 and 7, at a dose level of either

- 1 × 10^6 cells per kg body weight, to a maximum of 1 × 10^8 cells per infusion (cohort A), or
- 2 × 10^6 cells per kg body weight, to a maximum dose of 2 × 10^8 cells per infusion (cohort B).

The primary objective was to assess the safety and tolerability of CYP-001. The secondary objectives were to evaluate efficacy based on the proportion of participants who showed a complete response (CR), overall response (OR) and overall survival (OS) by day 28 and day 100.

Findings of the trial were that the 15 patients in the late stage of the disease with little or no chance of survival responded very well to CYP-001. Key highlights of the first 100 days included:

- OR by day 100 of 93%
- CR by day 100 of 53%
- OS at day 100 of at least 87%
- no treatment-related serious adverse events.

Exhibit 7 –Phase 1 trial design for CYP-001 in GvHD (completed)

Aim	The purpose of this study is to assess the safety, tolerability and efficacy of two infusions of CYP-001 in adults with steroid-resistant GvHD.
Summary design	16 pt Phase 1 clinical trial in Australia & the UK
Design details	16pts, male or female 18-75 years old **Dose administered:** Mesenchymoangioblast-derived mesenchymal stem cells (CYP-001) at a dose of 1 million cells/kg (up to a maximum of 100 million cells) by IV infusion on two occasions (Day 0 and Day 7). **Frequency and duration of administration:** Administered twice, on Day 0 and Day 7. **Mode of administration:** IV (Intravenous) infusion.
Primary endpoints	Incidence and severity of treatment emergent adverse events (28 days) and incidence and severity of serious adverse events deemed possibly related to CYP-001 (100 days)
Secondary endpoints	Proportion of participants who show a Complete Response (absence of any signs or symptoms of GvHD) by Day 28
Start date	Mar-17
Completion date	Jun-20

Source: Clinicaltrials.gov.

Final study results were published in (and featured on the front cover of) the prestigious journal *Nature Medicine* in September 2020. Successful completion of the Phase 1 trial of CYP-001 in GvHD represents a major development milestone for the company and with safety profile demonstrated allows Cynata to advance into Phase 2 trials for multiple indications.

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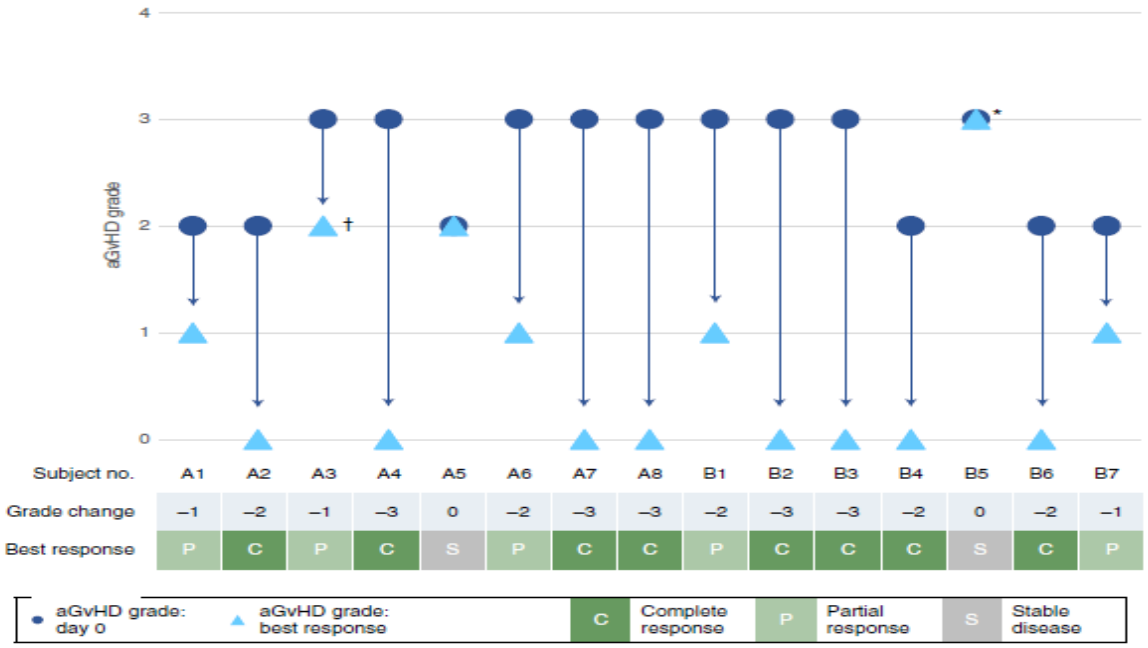
Exhibit 8 – GvHD Phase 1 trial results – met all clinical endpoints; support advancing to Phase 2



Source: Phase 1 trial published in *Nature Medicine,* September 2020.

Next steps in GvHD – Phase 2

A Phase 2 trial is currently planned in conjunction with development partner and licensee Fujifilm.

Competitive landscape in GvHD

Notwithstanding the approval and launch of Temcell in Japan, which we think validates the use of MSCs in aGvHD, MSC-based products for aGvHD have yet to be approved by the FDA.

Exhibit 9 – Competing development pipeline of treatments for GvHD (these include both prophylactic and post-surgical treatments)

Product	Company	Product type	Target date	Comments	Clinical ID	Phase
Alpha-1 antitrypsin (AAT)	CSL Behring	Protease inhibitor	Nov-23	Phase 3 - 122 participants, Male or Female aged >= 18 years. AAT administered once vs placebo with participants evaluated after 28 days.	NCT04167514	3
CD24Fc	OncoImmune, Inc.	Biological immunomodulator	Feb-24	Phase 3 - 180 participants, Male or Female aged >= 18 years. CD24Fc administered through IV infusion of days -1, 14 and 28 (480, 240 and 240 mg respectively) vs standard GvHD prophylaxis (Methylprednisolone & Prednisone).	NCT04095858	3
Itacitinib	Incyte Corporation	Janus kinase 1 (JAK1) inhibitor	Feb-25	Phase 3 - 431 participants, Male or Female aged >= 18 years. Intacitinib administered orally once daily over test (28 days) to identify appropriate doseage levels of drug vs GvHD prophylaxis.	NCT03584516	3
Natalizumab	Biogen	Steroid	Apr-22	Phase 2 - 90 participants, Male or Female aged >= 18 years. 300mg Natalizumab administered twice (Day 0 and 14) vs standard GvHD prophylaxis.	NCT02133924	2
EQ001	equillium	Monoclonal antibody	Feb-22	Phase 2 - 84 participants, Male or Female aged >= 12 years. EQ001 administered every two weeks for a total of 5 doses vs placebo.	NCT03763318	2
BMS-986004	Bristol-Myers Squibb	Humanised monoclonal antibody	Jan-24	Phase 2 - 45 participants, Male or Female aged >= 18 years. BMS-986004 administered through IV infusion every two weeks from Day -3 to 100 (three ascending dose levels examined, 225, 675 and 1500mg respectively) vs standard GvHD prophylaxis.	NCT03605927	2
RGI-2001	Regimmune Corporation	Liposomal formulation of alpha-GalCer	May-22	Phase 2 - 50 participants, Male or Female aged between 16 and 64. RGI-2001 administered six times weekly, 100µg/kg vs standard prophylaxis.	NCT04014790	2
Abatacept	Bristol-Myers Squibb	Immunomodulator	Dec-23	Phase 2 - 28 participants, Male or Female aged between 3 and 21. 8 doses of abatacept (10 mg/kg intravenously on days -1, +5, +14, +28, +56, +84, +112, and +150) vs conventional GvHD prophylaxis.	NCT03924401	2
Cyclophosphamide	Sanofi	Alkylating agent	Dec-21	Phase 2 - 80 participants, Male or Female aged between 18-70. Cyclophosphamide administered (50mg/kg) on days +3 and +4 vs Thymoglobulin (4.5mg/kg) on days -1, -1 and +1.	NCT04202835	2
Umbilical cord–derived mesenchymal stem cell	Cytopeutics Sdn. Bhd.	Mesenchymal stem cell	Dec-21	Phase 2 - 40 participants, Male or Female aged >= 16 years. Cyto-MSC (UC MSC) 5 million UCMSCs per kg bodyweight vs conventional treatment.	NCT03847844	2

Source: Clinicaltrials.gov.

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Strategic partnership for CYP-001 in GvHD – Fujifilm

Cynata and Fujifilm signed a non-binding development and commercialisation term sheet in September 2016 which then matured to a license option agreement in January 2017 involving the purchase of A$3.97m in Cynata shares at a 35% premium.

In 2019, Fujifilm exercised its option and exclusively licensed CYP-001 from Cynata worldwide. The terms of the transaction are as follows:

- Cynata received an upfront fee of US$3m.
- Fujifilm agreed to assume all future development costs, as well as to be responsible for regulatory submissions and commercialisation.
- On the completion of several future milestones, Cynata can earn up to US$43m. These milestones include
    - completion of the first Phase 2 clinical trial in USA, UK or Japan (US$2m)
    - completion of Phase 3 clinical trials (US$3m)
    - submission of applications for regulatory approvals (US$12m)
    - acceptance of geographic marketing authorisations and first sales (US$16m)
    - extending the indication (US$10m).
- Cynata will receive a royalty of 10% on future product sales if this commercialisation occurs in countries where licensed patents are granted or pending.

Cynata has several obligations to WARF as a result of this transaction:

- one-off cash payment of US$10,000
- mid-single-digit percentage royalty on Fujifilm product sales
- 30% of other amounts received from Fujifilm (including milestone payments).

The investment made Fujifilm the then largest shareholder of Cynata with a 10% holding at that time.

Cynata has indicated that it views Fujifilm exercising its licence option as a validation of its Cymerus™ platform technology, and that it sees this step as supporting continued commercialisation of its products across other indications.

Orphan Drug Designation

CYP-001 was granted Orphan Drug Designation in March 2018 by the FDA for the treatment of aGvHD.

The Orphan Drug Designation Program was established in 1983 and provides orphan status to drugs and biologics which are defined as those intended for the safe and effective treatment, diagnosis, or prevention of rare diseases/disorders that affect:

- fewer than 200,000 people in the US, or
- more than 200,000 people, but for which drug companies would not be expected to recover the costs of developing and marketing a treatment drug.

This means that if CYP-001 reaches the market before another product considered by the FDA to be ‘the same drug’, this could provide seven years of exclusivity from the date of approval. Notably, Mesoblast with Remestemcel-L is pursuing approval from the FDA – however, at this point, its initial BLA has not secured the company an approval.

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Knee Osteoarthritis (CYP-004): Huge Unmet Need, and the Largest KO Trial to Date

Disease overview and market opportunity

Osteoarthritis (OA) is a degenerative joint disease which is characterised by the breakdown of cartilage within joints. This results in bones rubbing together, creating stiffness, pain, and impaired movement. It is considered an age-related disease stemming from wear and tear of joints from repetitive use, exacerbated by gender (more common in women), obesity, injury, race, and occupation.

The disease is the most common cause of disability in adults 60 years of age and older, and mainly affects the hands, knees, and hips. In Australia, knee osteoarthritis (KO) is the leading cause of lower limb disability in older people, affecting more than 2m people. There is no cure for KO and while the primary therapeutic focus has been on the management of the resultant pain and disability, treatment often leads to costly joint replacement.

According to the Centers for Disease Control and Prevention (CDC), over 32.5m adults have OA in the US. According to the *Lancet*, the global prevalence of KO is 14%–18%.

Rationale – pre-clinical evidence that MSCs can modify disease progression

The body's natural response to tissue repair in synovial joints (such as the knee, hip, or elbow) is to deploy inflammatory cells to the damaged tissue, causing the release of growth factors and other molecules. Unfortunately, this response over time exacerbates the problem with a paradoxical degeneration of the joint instead of regeneration. Preclinical studies demonstrate that these proteins attract stem cells that proliferate and can differentiate into chondrocytes (cartilage cells), producing large amounts of cartilage matrix[5]. Furthermore, some stem cells differentiate into endothelial cells and produce new blood vessels to nourish the chondrocytes and damaged cartilage. By increasing the stem cells within the joint, as a source of cytokines/growth factors to stimulate resident cells, it is thought to be possible to increase matrix deposition (tissue formation) and therefore accelerate the quality and rate of regeneration of the compromised cartilage.

Clinical – Phase 3 trial underway

The Phase 3 trial of CYP-004, Cynata's Cymerus™ MSC product candidate for OA, is the largest study of MSCs in this indication to date worldwide. The trial is taking place at study centres in Sydney and Tasmania. The project is being led by Professor David Hunter. Professor Hunter is the Florance and Cope Chair of Rheumatology and Professor of Medicine at the University of Sydney. The project is funded by an NHMRC project grant.

Exhibit 10 – SCUlpTOR1 - Knee osteoarthritis Phase 3 clinical trial

Clinical trial underway, sponsored by the University of Sydney and funded by an NHMRC project grant	
Aim	Evaluating the efficacy and cost-effectiveness of stem cell injections in people with mild to moderate knee osteoarthritis: a randomised placebo-controlled trial (the SCUlpTOR trial)
Summary design	440 pt Phase 3 clinical trial in Australia (NSW, TAS)
Design details	440 pts; Male or Female >=40 years of age. **Dose administered**: 2.5 x 10^7 cell culture-expanded mesenchymoangioblast-derived mesenchymal stem cells (MSCs) suspended in 5 ml excipient solution. **Frequency and duration of administration**: three knee intra-articular injections of allogeneic MSCs performed at baseline, week 3 and 52 (12-months). **Mode of administration:** ultrasound-guided intra-articular injections applied to the study knee delivered by an experienced radiologist.
Primary endpoints	Proportion of participants achieving patient-acceptable symptom state (PASS) for knee pain.
Secondary endpoints	Knee pain intensity measured by the visual analogue scale (VAS).
Start date	Mar-21
Completion date (anticipated)	Sep-24

Source: Australian New Zealand Clinical Trials Registry.

[5] Role of stem cell therapy in orthopaedic tissue engineering and regenerative medicine – Moshiri et al (2013)

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The trial is a randomised, double-blind placebo-controlled trial, seeking to enrol 440 patients with KO. Participants will receive intra-articular injections of Cymerus™ MSCs or placebo on three occasions over a period of one year and will be followed up for a total of two years from enrolment. The co-primary endpoints are: (i) the proportion of participants achieving patient-acceptable symptom state (PASS) for knee pain at 24 months; and (ii) central medial femorotibial (cMFT) cartilage loss from baseline to 24 months. Secondary outcome measures will include assessments of pain, other symptoms, physical function and quality of life. The trial is now underway, having commenced patient recruitment in November 2020.

Competitive landscape

While there are some disease-modifying contenders in the pipeline of competitors, we do not believe Cynata has any direct competitors in this indication. As such, Cynata's Cymerus™ MSC product could be the first biologic approved in this indication with a multifaceted approach to both inflammation and regeneration in OA.

Exhibit 11 – Competing development pipeline of treatments for knee osteoarthritis

Product	Company	Product type	Target date	Comment	Clinical ID	Ph
Lorecivivint	Biosplice Therapeutics, Inc.	Intra-articular potential disease modifying drug	Sep-22	Phase 3 - 500 participants, one dose of 0.07mg of lorecivivint or placebo - evaluation at 24 & 48 weeks.	NCT04520607	3
Esflurbiprofen	Taisho Pharmaceutical Co., Ltd.	Nonsteroidal anti-inflammatory drug	Mar-21	Phase 3 - 312 participants => 40 years old, one dose (plaster) containging 40mg of Esflurbiprofen.	NCT03434197	3
Amniotic Suspension Allograft	Organogenesis	Human amniotic membrane	Jun-23	Phase 3 - 474 participants => 18 years old, single intra-articular injection of 2mL of ASA + 2mL of saline or placebo.	NCT04636229	3
Diclofenac sodium active topical patch	Noven Pharmaceuticals, Inc.	Nonsteroidal anti-inflammatory drug	Aug-22	Phase 3 - 352 participants, Male or Female aged 40-85 years, one patch applied with diclofenac sodium will be evaluated against the placebo patch over 12 weeks.	NCT04683627	3
Cingal	Anika Therapeutics, Inc.	Viscoelastic supplement	Nov-21	Phase 2 - 231 participants, Male or Female aged 30-75 years, 4-mL unit dose elavuated vs saline over 26 weeks.	NCT04231318	3
Triamcinolone Hexacetonide - Lederlon	Anika Therapeutics, Inc.	Intra-articular potential disease modifying drug	Nov-21	Phase 2 - 231 participants, Male or Female aged 30-75 years, 1-mL unit dose evaluated vs saline over 26 weeks.	NCT04231318	3
MEDI7352	AstraZeneca	Bi-specific fusion protein	Dec-22	Phase 2 - 300 participants, Male or Female aged 18-80 years, 6 doses of MEDI7352 over 12 weeks.	NCT04675034	3
LNA043	Novartis Pharmaceuticals	Modified human angiopoietin-like 3 (ANGPTL3) protein	Aug-22	Phase 2 - 131 participants, Male or Female aged 18-55 years, single intra-articular injection of 20-40mg of LNA043 or placebo.	NCT03275064	2
LRX712	Novartis Pharmaceuticals	Cartilage anabolic	May-23	Phase 2 - 40 participants, Male or Female aged 35-75 years, multiple intra-articular injections of LRX712 or placebo.	NCT04097379	2
ATB-346	Antibe Therapeutics Inc.	Nonsteroidal anti-inflammatory drug	N/A	Phase 2/3 - 360 participants, Male or Female aged 40-75 years, once daily (150-250mg) injection of ATB-346 over 14 days vs placebo.	NCT03978208	2

Source: Clinicaltrials.gov.

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COVID-19–related Respiratory Failure (CYP-001): Right Place, Right Time

Disease overview and market opportunity

Respiratory failure can result from nearly any condition that affects breathing function or lungs themselves, leading to the failure of the lung function. One such condition is acute respiratory distress syndrome (ARDS) which causes fluid to build up in the lungs so the air sacs cannot property exchange carbon dioxide for oxygen. ARDS is a severe inflammatory condition triggered by an exaggerated immune response. Causes of ARDS vary and include pneumonia, sepsis (an overwhelming infection in the body), trauma, cytokine release syndrome and more recently COVID-19. No specific therapy exists to treat this disorder currently. Supportive care is typically given in an intensive care unit (ICU) setting along with mechanical ventilation and including extracorporeal membrane oxygenation (ECMO). ECMO circulates blood through an artificial lung, oxygenating the blood before putting it back in the patient's bloodstream.

ARDS accounts for 10% of all ICU admissions, and ~25% of patients require mechanical ventilation. According to the ARDS Foundation, about 150,000 cases of ARDS are reported per year in the US. Historically about 40%–60% of patients die from ARDS, although we assume this number to be much higher recently given the COVID-19 pandemic.

Rationale: positive preclinical data in large animal study

Cymerus™ MSCs have shown favourable preclinical evidence in a large animal study. In a randomised study of 14 sheep with severe ARDS, supported by ECMO, a single endo-brachial infusion of Cymerus™ MSCs was given. The patient was then monitored for 24 hours. The study showed reduced severity of lung injury and a reduction in circulatory shock associated with ARDS, with no adverse effects on renal or liver function. Data from this study has now been published in a peer-reviewed journal[6]. Stem cell–based therapy is a potentially attractive option for treating patients with ARDS because the mechanisms of efficacy are mediated by several pathways that may reduce the severity and enhance the recovery from lung injury.

Clinical: Phase 2 trial (first patient enrolled in Cynata's MEND clinical trial)

A Phase 2 study (Exhibit 12) initiated in August 2020, targeting the enrolment of 24 patients, is being conducted at centres in NSW and Victoria in collaboration with the Cerebral Palsy Alliance Research Institute and COVID-19 Stem Cell Treatment (CSCT) Group investigators. This is an open-label, randomised, controlled clinical study with patients randomised on a 1:1 basis. Patients who receive CYP-001 will receive an IV infusion of 2m Cymerus™ MSCs/kg of body weight (maximum 200m cells). The primary endpoint will be a measure of hypoxemia (low blood oxygen level caused by compromised lung function) at 7 days post treatment, as well as safety and tolerability after 28 days. Results could demonstrate potential relevance in diseases including ARDS, Cytokine Release Syndrome (CRS) and sepsis.

Exhibit 12 – MEND (MEseNchymal coviD-19) Trial

Pilot, multi-centre, open-label trial underway, in collaboration with Cerebral Palsy Alliance	
Aim	Assess the early efficacy of intravenous (IV) administration of CYP-001 in adults admitted to an intensive care unit (ICU) with respiratory failure
Summary design	24 pt Phase 2 clinical trial in Australia (NSW, VIC)
Design details	24 pts; Male or Female >= 18 years old. **Dose administstered:** Each Pt randomised to receive CYP-001 will receive an IV infusion of 2 million Cymerus mesenchymal stem cells (MSCs)/kg of body weight. **Frequency and duration of administration:** Administered twice on D1 and D3 of trial. **Mode of adminstration:** Intravenous administration by professional.
Primary endpoints	Trend in trajectory of PaO2/FiO2 ratio (P/F ratio) between groups. The P/F ratio is a powerful objective tool to identify acute hypoxemic respiratory failure when supplemental oxygen has already been administered and no room air ABG is available, or pulse oximetry readings are unreliable.
Secondary endpoints	Incidence and severity of treatment-emergent adverse events and change in C-reactive protein (CRP) levels
Start date	Aug-20
Completion date (anticipated)	Dec-21

Source: Clinicaltrials.gov.

6 Millar et al 2020, 'Combined Mesenchymal Stromal Cell Therapy and Extracorporeal Membrane Oxygenation in Acute Respiratory Distress Syndrome. A Randomized Controlled Trial in Sheep', https://doi.org/10.1164/rccm.201911-2143OC.

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Cynata recently received ethics committee approval to expand the recruitment criteria of the MEND trial in patients in intensive care with respiratory failure, to include other causes beyond COVID-19 (such as influenza), which the company expects will significantly accelerate recruitment.

Competitive landscape

Pipeline competitor technologies include other MSC product developers (Athersys, Mesoblast) which underscores the potential for MSCs in this indication.

Exhibit 13 – Competing development pipeline of treatments for COVID-19–related ARDs

Product	Company	Product type	Target date	Comments	Clinical ID	Phase
FP-025	Foresee Pharmaceuticals Co., Ltd.	MMP 12 inhibitor	Feb-22	Phase 3 - 403 participants, Male or Female aged >= 18 years old. 300mg FP-025 administered once vs placebo.	NCT04750278	3
Brexanolone	Sage Therapeutics	Synthetic neuroactive steroid gamma-aminobutyric acid	Oct-21	Phase 3 - 100 participants, Male or Female aged >= 18 years old. Single, continuous, IV infusion of brexanole for 60 hours vs placebo.	NCT04537806	3
MultiStem	Athersys, Inc	Multipotent adult progenitor cell	Dec-23	Phase 3 - 400 participants, Male or Female aged between 18-89 years old. IV infusion of multistem vs placebo, evaluating ventilator free days between day 0 and 28.	NCT04367077	3
EB05 IV	Edesa Biotech Inc.	Monoclonal antibody	Apr-21	Phase 2 - 396 participants, Male or Female aged >= 18 years. 300mg. Standard of care + single IV infusions (15mg/kg) of EB05 vs placebo.	NCT04401475	2
PLN-74809	Pliant Therapeutics, Inc.	Dual selective inhibitor	Oct-21	Phase 2 - 36 participants, Male or Female aged >= 18 years.Three cohorts given ascending, singular dose of PLN-74809 vs placebo.	NCT04565249	2
EC-18	Enzychem Lifesciences Corporation	Monoacetyldiglyceride	Nov-21	Phase 2 - 60 participants, Male or Female aged >= 18 years old. 2000mg of EC-18 daily vs placebo over 28 days. Evaluating patients free from respiratory failure at day 28.	NCT04569227	2
Lucinactant	Windtree Therapeutics	Synthetic surfactant	Jul-21	Phase 2 - 20 participants, Male or Female aged between 18 and 75 years. Lucinactant 80mg (TPL)/kg administered once, evaluating safety over 12 hours and through day 30.	NCT04389671	2
PLX-PAD	Pluristem Ltd.	Placenta-derived stromal cells	Mar-22	Phase 2 - 140 participants, Male or Female aged between 40 and 80 years. 3 cohorts - low dose, high dose and interval high dose. Participants in interval high dose will be treated twice with a 1mL injection weekly vs placebo.	NCT04389450	2
APL-9	Apellis Pharmaceuticals, Inc.	Peptide	Jan-21	Phase 2 - 66 participants, Male or Female aged >= 18 years. 180mg of ALP-9 + Standard of care vs placebo.	NCT04402060	2
PF-06650833	Pfizer	Orally active inhibitor	Dec-21	Phase 2 - 68 participants, Male or Female aged between 18 and 75 years. 200mg IR suspension formulation every 6 hours in addition to Standard of care therapy over day 0 to 29 vs placebo.	NCT04575610	2

Source: Clinicaltrials.gov.

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Critical Limb Ischemia (CYP-002): Phase 2 Ready with Ethics Approval Confirmed

Disease and market opportunity

Critical limb ischemia (CLI) is an advanced, typically end-stage form of peripheral artery disease (PAD), a common circulation problem that occurs when arteries that carry blood throughout the body become narrowed or blocked, restricting blood flow to legs and feet. Causes of CLI include smoking, diabetes, chronic kidney disease, high blood pressure and high cholesterol. Left untreated, CLI can lead to tissue loss, gangrene, amputations and eventually death.

The principle that characterises the therapeutic application of stem cells is the restoration of vascular cellularity, the control and the support of the newly formed vessels which must ensure an adequate supply of oxygen in critical ischemic areas (areas which are critically undersupplied with blood). Studies indicate that clinical benefits from the use of stem cells in CLI include improvement in transcutaneous partial pressure of oxygen, reduction of pain and reduced rates of limb amputation.

The prevalence of CLI in the US is estimated at 2m,[7] with this number likely to rise given trends in important risk factors such as age, diabetes, and smoking. Around 25% of CLI patients who are unable to undergo vascular surgery to treat the condition die within a year of diagnosis. More than 60% of patients with CLI die within 5 years of diagnosis.

Rationale – positive preclinical data in mouse study

Cymerus™ MSCs have shown favourable preclinical evidence in a mouse study. In the 19-mouse study hindlimb ischemia was created by ligating the left common iliac artery and vein and ligating and severing the femoral artery. Adductor muscles on the ischaemic leg were then injected with either Cymerus™ MSCs (n=10) or a saline injection control (n=9) immediately after surgery. Over a four-week follow-up period, the return of blood flow to the lower limb was measured, using a laser Doppler flow technique. Results showed Cymerus™ MSCs improved limb blood flow, reduced necrosis and maintained muscle mass and gross muscle appearance. The study concluded that MCA-derived MSCs have a significant and protective effect against ischemic insult. Data from this study has been published in a peer-reviewed journal.[8]

Clinical – Phase 2 trial ready

Cynata received approval from the UK Medicines and Healthcare Products Regulatory Agency (MHRA) to proceed with a 90-patient Phase 2 clinical trial of Cymerus™ MSC product CYP-002 in patients with CLI. Preclinical data from the use of Cymerus™ MSCs in CLI was positive with reports of improved limb blood flow, reduced necrosis and protection against muscle damage, fibrosis, and limb loss. Cynata anticipates conducting the clinical trial at multiple centres in the UK and Australia; however, timing has yet to be announced following delays arising from the COVID-19 pandemic.

[7] The burden of critical limb ischemia: a review of recent literature -S.Duff et al (2019)

[8] Koch et al 2015, 'Mesenchymoangioblast-derived mesenchymal stromal cells inhibit cell damage, tissue damage and improve peripheral blood flow following hindlimb ischemic injury in mice', https://doi.org/10.1016/j.jcyt.2015.10.013.

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Exhibit 14 – Phase 2 trial design for CYP-002 in critical limb ischemia

Aim	A randomised, double-blind, placebo-controlled Phase 2 study to investigate the efficacy, safety and tolerability of CYP-002 in adults with critical limb ischaemia who are unsuitable for revascularisation
Summary design	Phase 2 clinical trial in Australia
Design details	90 pts; Male or Female >= 45 years of age. **Dose administered:** Pts randomised into three groups - placebo - IV infusion of 50 or 100 million Cymerus mesenchymal stem cells (MSCs)/kg of body weight. **Frequency of administration:** Treatments administered on a single occasion at beginning of trial. **Mode of administration:** Intramuscular injection into the study limb.
Primary endpoints	To evaluate the efficacy of CYP-002 in adults with CLI, based on improvement in Rutherford Classification up to 12 months after treatment; and to assess the safety and tolerability of CYP-002 in adults with CLI, up to 12 months after treatment.
Secondary endpoints	To evaluate the efficacy of CYP-002 in adults with CLI, based on different outcome measures at various timepoints up to 24 months after treatment; and to further assess the safety and tolerability of CYP-002 in adults with CLI up to 24 months after treatment.
Start date	Dec-19
Completion date (anticipated)	N/A

Source: Clinicaltrials.gov.

Competitive landscape

The competitor pipeline contains a variety of approaches including revascularising interventions or autologous derived MSCs. Potentially there are two relatively close competitors in Fate Therapeutics and BlueRock. However, both are in Phase 1 stage of clinical development compared to Cynata's Phase 2–ready program.

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Exhibit 15 – Competing development pipeline of treatments for critical limb ischemia

Product	Company	Product type	Comments	Target date	Clinical ID	Phase
Evolocumab	Amgen	PCSK9 inhibitor	Phase 4 - 32 participants, Male or Female aged between 40-85 years. Evolocumab 140mg/mL Injector 1milliliter (mL) Pen x 3 for a monthly dose of 420 mg for 12 months vs placebo.	Feb-22	NCT04306471	4
StellarexTM	Spectranetics Corporation	Angioplasty balloon	Phase 4 - 75 participants, Male or Female aged >= 18 years. Balloon indicated for the treatment vs no treatment. Evaluation of limb salvage through 6 months or major amputation through 30 days.	Aug-26	NCT03395236	4
NL003	Beijing Northland Biotech. Co.	DNA plasmid	Phase 3 - 300 participants, Male or Female aged between 20-80 years. Participants subject to 8mg of of NL003 on Day 0, 14 and 28 vs placebo.	Mar-22	NCT04275323	3
Apixaban	Pfizer	Anticoagulant	Phase 3 - 200 participants, Male or Female aged >= 18 years. 2.5mg twice daily for one year vs ASA (Competitor drug) - evaluation of restenosis and major amputation over 12 months.	May-22	NCT04229264	3
REX-001	Ixaka Ltd	Autologous bone marrow mononuclear cells	Phase 2 - 78 participants, Male or Female aged between 18-85 years. REX-001 administered through an inter-arterial catheter vs placebo, evaluation of healing of ischemic ulcers on the index leg after 12 months.	Jul-23	NCT03174522	3
ACP-01	Hemostemix	Autologous cell therapy	Phase 2 - 95 participants, Male or Female aged >= 18 years. Singular injection of ACP-01 into lower extremity vs placebo. Evaluation of wound size, amputation and survival levels after 12 months.	Dec-20	NCT02551679	2
CLBS12	Caladrius Biosciences, Inc.	Autologous cell therapy	Phase 2 - 35 participants, Male or Female aged between 20 and 85. Intramuscular transfusion of CLBS12 vs standard of care. Time to continuous CLI-free status assessed after 12 months.	Jun-21	NCT02501018	2
YQ23	New Beta Innovation Limited (not listed)	Immodulator	Phase 2 - 51 participants, Male or Female aged >= 18 years. Single dose of 120 mg/kg YQ23 via intravenous route vs placebo used to evaluate safety and tolerability of YQ23.	Sep-23	NCT04792008	2
AAV-hTERT	Libella Gene Therapeutics	Adenoviral gene therapy	Phase 1 - 5 participants, Male or Female aged >= 45 years. Single treatment of AAV-hTERT via IV administration used to evaluate incidence of serious adverse events over 12 months.	Dec-20	NCT04110964	1
cBMA aspirate	Zimmer Biomet	Concentrated bone marrow aspirate	Phase 1 - 12 participants, Female aged between 40 and 90. Injection of cBMA into the anterior tibialis muscle and upper index leg of subjects scheduled for semi-elective BKA 7-21 days before surgery. Evaluation of incidence of serious adverse events over 12 months.	Jul-23	NCT02863926	1
FT500	Fate Therapeutics	iPSC-derived NK cell product	Phase 1 - 76 participants, Male or Female aged >= 18 years. Three cohorts - FT500 once weekly for 3 weeks, FT500 once weekly for 3 weeks in combination with immune checkpoint inhibitors, FT500 +IL-2 once weekly for 3 weeks with immune checkpoint inhibitors. Evaluating the incidince of subjects with dose limiting toxicities within each dose level cohort.	Jun-22	NCT03841110	1
MSK-DA01	BlueRock	Induced pluripotent stem cell (iPSC)	Phase 1 - 10 participants, Male or Female aged between 60-75 years. Evaulation of the incidence of serious adverse events at 1 year post transplant or abnormal tissue or overgrowth related to presence of transplanted cells.	Nov-23	NCT04802733	1

Source: Clinicaltrials.gov.

Diabetic Foot Ulcers (MSC-seeded silicon dressing): MSCs for topical application

In March 2021, Cynata entered into a licence agreement with TekCyte P/L to use its proprietary surface modification technology to product polymer-coated dressings for the delivery of MSCs to wounds. Studies of Cymerus™ MSCs in a preclinical model of diabetic wounds, typically diabetic foot ulcers or DFUs, showed promising signs of efficacy.

Diabetic foot ulcers, or DFUs, are one of the most severe consequences of diabetes. The global prevalence of diabetic foot ulcers in diabetic patients varies from 3% in Oceania to 13% in North America, with a global average of 6.4%. The condition is more frequent in older patients. The annual incidence of diabetic foot ulcer or necrosis in diabetic patients is known to be about 2% to 5%, and the lifetime risk ranges from 15% to 20%.

Cynata plans to commence phase 1/2 trials of the topically applied MSC-seeded silicon dressing in 2HCY21.

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Competitive Landscape

Cynata's competitive landscape includes both MSC-based therapeutic developers and all other drug development companies targeting the same indications as Cynata. Given their multipotent properties, clinical research into therapeutic and regenerative applications of MSCs as highlighted in Exhibit 16 are numerous and varied. More than 1,050 clinical trials are registered at FDA.gov exploring MSC applications for a broad range of indications. That said, most of the clinical-stage MSC therapies have been unable to meet primary efficacy end points and in general have been hampered by the shortcomings of conventionally manufactured MSCs. We think this presents Cynata with an opportunity to step in with a more robust MSC product whose efficacy/potency has been preserved by virtue of its innovative and novel Cymerus™ technology manufacturing process.

Cynata's MSC competitors by indication are shown in Exhibit 17.

Exhibit 16 – Representative indications of MSCs in clinical trials

General Indication	Company	Product	Clinical indication	Cell source		Administration route	Clinical efficacy (Y/N)	Engineered (Y/N)	Year started	Phase	Status	Trial number
Cancer	Apceth GmbH & Co. KG	MSC_apceth_101	Advanced gastrointestinal cancer	Autologous	BM_3	Systemic	N	Y	2013	1	Terminated	NCT02008539
Cardiac disorders	Mesoblast, Inc.	Prochymal®	Acute mycardial infarction	Allogeneic	BM_3	Systemic	Y	N	2009	2	Complete	NCT00877903
	Mesoblast, Inc.	Rexlemestrocel-L	Chronic heart failure	Allogeneic	MPC-BM_4	Local	Y	N	2014	3	Ongoing, not recruiting	NCT02032004
	Athersys, Inc	MultiStem	Ischemic stroke	Allogeneic	BM_3	Systemic	N	N	2011	2	Complete	NCT01436487
GcHD	Mesoblast, Inc.	Prochymal	Grade B to D acute GvHD	Allogeneic	BM_3	Systemic	Y	N	2006	3	Complete	NCT00366145
	Mesoblast, Inc.	Remestemcel-L	Grade B to D acute GvHD	Allogeneic	BM_3	Systemic	Y	N	2015	3	Complete	NCT02336230
IBD	Tigenix S.A.U.	Cx601	Crohn's disease	Allogeneic	AT_5	Local	Y	N	2012	3	Complete	NCT01541579
	Mesoblast, Inc.	Prochymal®	Crohn's disease	Allogeneic	BM_3	Systemic	TBD	N	2007	3	Ongoing, not recruiting	NCT00482092
	Pfizer	MultiStem	Ulcerative colitis	Allogeneic	BM_3	Systemic	N	N	2010	2	Complete	NCT01240915
	AlloCure Inc.	AC607	Acute kidney injury	Allogeneic	BM_3	Systemic	N	N	2012	2	Terminated	NCT01602328
Kidney disorders	Mesoblast, Inc.	Mesenchymal Precursor Cells	Diabetic nephropathy	Allogeneic	MPC-BM_4	Systemic	Y	N	2013	1/2	Complete	NCT01843387
Neurodegenerative disease	Brainstorm-Cell Therapeutics	NurOwn	ALS	Autologous	BM_3	Local	Y	Y	2013	2	Complete	NCT02017912
	Brainstorm-Cell Therapeutics	NurOwn	Chronic progressive MS	Autologous	BM_3	Local	TBD	Y	2019	2	Recruiting	NCT03799718
	Mesoblast, Ltd.	Mesenchymal Stem Cells	Degenerative disc disease	Allogeneic	MPC_1	Local	Y	N	2011	2	Complete	NCT01290367
Respiratory disorders	Mesoblast, Inc.	Prochymal® (Osiris)	Chronic obstructive pulmonary disease	Allogeneic	BM_3	Systemic	N	N	2008	2	Complete	NCT00683722

Source: Shattering barriers toward clinically meaningful MSC therapies – Levy et al (2020).

Exhibit 17 – MSC products that have received regulatory approval

Name	MSC Type	Indication	Country of Approval (Year)	Company
Alofisel	Human AT-MSC	Complex perianal fistulas in CD	Europe (2018)	TiGenix NV/Takeda
Prochymal (remestemcel-L)	Human BM-MSC	GvHD	Canada (2012) New Zealand (2012)	Osiris Therapeutics Inc./ Mesoblast Ltd
Temcell HS Inj	Human BM-MSC	GvHD	Japan (2015)	JCR Pharmaceuticals
Queencell	Human AT-MSC	Subcutaneous tissue defects	South Korea (2010)	Anterogen Co. Ltd.
Cupistem	Human AT-MSC	Crohn's fistula	South Korea (2012)	Anterogen Co. Ltd.
Neuronata-R	Human BM-MSC	Amytrophic lateral sclerosis	South Korea (2014)	Corestem Inc.
Cartistem	Human UC-MSC	Knee articular cartilage defects	South Korea (2012)	Medipost Co. Ltd.
Stemirac	Human BM-MSC	Spinal cord injury	Japan (2018)	Nipro Corp.
Stempeucel	Human BM-MSC	Critical limb ischemia	India (2016)	Stempeutics Research PVT
Cellgram-AMI	Human BM-MSC	Acute MI	South Korea (2011)	Pharmicell Co. Ltd.

Source: Shattering barriers toward clinically meaningful MSC therapies – Levy et al (2020).

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Intellectual Property: Patents and Other Assets

Cynata's core patent portfolio contains a combination of granted and pending patents across three broad patent families. Two patent families are owned by the Wisconsin Alumni Research Foundation (WARF), and licensed to Cynata. The remaining patent family contains patents for which Cynata has filed. A further series of patents has been licensed to Cynata by Cellular Dynamics International (now Fujifilm Cellular Dynamics, Inc.) relating to processes to derive iPSCs.

1. Non-Exclusively Licensed to Cynata by WARF

- 1.1 Serum-free cultivation of primate embryonic stem cells: James A Thomson: 22 granted/validated patents globally

2. Exclusively Licensed to Cynata by WARF

- 2.1 Generation of Clonal Mesenchymal Progenitors and Mesenchymal Stem Cell Lines Under Serum-Free Conditions: Maksym Vodyanyk, Igor Slukvin: 18 granted/validated patents globally
- 2.2 Methods and Materials for Hematoendothelial Differentiation of Human Pluripotent Stem Cells Under Defined Conditions: Igor Slukvin, Gene Uenishi: 31 granted/validated patents and 4 pending patents globally

3. Cynata: Wholly Owned

This group contains four patent families.

- 3.1 P100952 Family – Colony-Forming Medium and Use Thereof: 3 provisional and 13 pending patents
- 3.2 P104383 Family – Pluripotent Stem Cell Assay: 1 provisional and 13 pending patents
- 3.3 P106784 Family – Method for Treating Allergic Airways Disease (AAD)/Asthma: 1 provisional and 14 pending patents
- 3.4 P110775 Family – Method for Improving Angiogenic Potential of a Mesenchymal Stem Cell: 1 provisional and 2 pending patents; 11 patents with filing in progress

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Financials

Cynata is in a strong financial position with A$28.2m in cash as at 31 March 2021. This included approximately A$1.4m R&D tax incentive refund received and A$3.3m capital raised via non-renounceable entitlement offer during the quarter and added to the A$15m raised via an institutional placement in 2QFY21. Management has indicated this should support R&D activities through to 2023 given the company's partnering model for both preclinical and clinical development of product candidates. Exhibit 18 highlights our financial forecasts for Cynata which include risk adjusted revenues from the commercialisation of CYP-001 in Japan which we have assumed will commence in FY23.

Exhibit 18 – Financial Summary

Financial Summary (AUD 000's)	FY19a	FY20a	FY21e	FY22e	FY23e	FY24e
PROFIT & LOSS						
Total Revenue	1,308,552	7,011,553	1,468,492	1,391,000	5,375,615	7,251,732
Total expenses	-10,041,249	-10,793,003	-10,487,298	-10,487,298	-10,487,298	-10,487,298
EBITDA	-8,452,732	-3,500,718	-8,738,074	-8,815,566	-4,830,950	-2,954,834
EBIT	-8,732,697	-3,781,450	-9,018,806	-9,096,298	-5,111,682	-3,235,566
Tax	0	0	0	0	0	0
NPAT	-8,472,146	-3,639,100	-8,876,456	-8,953,948	-4,870,117	-3,084,729
Minority Interest	0	0	0	0	0	0
Shares Outstanding (m)	101.9	117.1	138.6	138.6	138.6	138.6
EPS (Underlying) cps	-8.48	-3.48	-7.58	-6.46	-3.51	-2.23
Dividend per share (cps)	0	0	0	0	0	0
BALANCE SHEET						
Current Assets	7,330,498	13,850,689	23,364,238	14,664,509	10,024,601	7,148,341
Cash	6,977,390	13,649,644	23,163,193	14,463,464	9,823,556	6,947,296
Receivables	67,044	16,965	16,965	16,965	16,965	16,965
Inventory	0	0	0	0	0	0
Other Assets	286,064	184,080	184,080	184,080	184,080	184,080
Non-Current Assets	4,919,246	3,630,151	3,349,419	3,095,200	2,864,991	2,656,523
PP&E	0	0	0	0	0	0
Intangibles	3,253,227	2,972,495	2,691,763	2,437,544	2,207,335	1,998,867
Other Non-current Assets	1,666,019	657,656	657,656	657,656	657,656	657,656
Current Liabilities	1,278,278	689,736	689,736	689,736	689,736	689,736
Payables	1,236,983	634,754	634,754	634,754	634,754	634,754
Short Term Debt	0	0	0	0	0	0
Provisions & Tax	41,295	54,982	54,982	54,982	54,982	54,982
Other financial liabilities	0	0	0	0	0	0
Non-Current Liabilities	0	0	0	0	0	0
Long Term Debt	0	0	0	0	0	0
Provisions	0	0	0	0	0	0
Other financial liabilities	0	0	0	0	0	0
Net Assets	10,971,466	16,791,104	26,023,921	17,069,973	12,199,856	9,115,12
Share Capital	47,987,688	57,165,390	75,472,390	75,472,390	75,472,390	75,472,390
Reserves	4,501,410	4,782,446	4,782,446	4,782,446	4,782,446	4,782,446
Retained Earnings	-41,522,356	-45,161,456	-54,235,640	-63,189,587	-68,059,704	-71,144,432
Minority Interests	0	0	0	0	0	0
Total Equity	10,971,466	16,791,104	26,023,921	17,069,973	12,199,856	9,115,12
CASH FLOW						
Operating Cash Flow	-6,759,077	-3,387,679	-8,595,724	-8,699,729	-4,639,907	-2,876,261
Capex	0	0	0	0	0	0
Acquisitions	0	0	0	0	0	0
Investing Cash Flow	0	0	0	0	0	0
Equity Issued	1,405,929	9,382,110	18,307,000	0	0	0
Debt Issued	0	0	0	0	0	0
Dividends	0	0	0	0	0	0
Financing Cash Flow	1,530,415	10,059,948	18,109,272	0	0	0
Change in Cash Balance	-5,228,662	6,672,269	9,513,549	-8,699,729	-4,639,907	-2,876,261

Source: Cynata, MST Access.

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Valuation

We value Cynata Therapeutics at A$408m or A$2.95 per share on an undiluted basis, using a risk-adjusted net present value (rNPV) method to discount future cash flows through to 2034, consistent with the expiry of current patent families. There are currently 3,165,557 options outstanding, exercisable at various prices and all currently out of the money. Our fair value of the shares on a fully diluted (141,729,856 shares) basis is A$2.89 per share.

Cynata's strategic focus on aGvHD has delivered proof of safety, signs of efficacy, a major strategic partner in Fujifilm and paved the way for Cynata to move into Phase 2 trials on several clinical fronts supported by strong preclinical data. As such, our valuation is based on five clinical candidates targeting major unmet medical in mainly inflammation and immune related diseases, namely aGvHD, osteoarthritis, respiratory failure (including patients with COVID-19 and influenza), critical limb ischemia and diabetic foot ulcers. We assume currently non partnered product candidates will attract a licensor at the conclusion of Phase 2 and apply a likelihood of approval (LOA) consistent with published biotechnology industry data related clinical development success rates of biologics[9].

Based on the Fujifilm alliance and an accelerated approval system for commercialisation of cell therapy products in Japan, we expect Cynata to first market CYP-001 in that country. Japan introduced an approval path for stem cell treatments in 2014 that avoids the phase 1 to 3 clinical trial system. In Japan, a cell therapy product can gain conditional market approval based on safety and efficacy signals on small numbers of patients, complemented by a five-to seven-year period of post marketing surveillance.

The breakdown of our rNPV model, which includes A$28.2m in net cash as reported at end of March 2021, and using a 13.5% discount rate, is shown in Exhibit 19. Our valuation assumes all non-partnered programs will be out licensed in Phase 2 with upfront payments of US$40m and all subsequent costs (R&D, launch and marketing) paid by the licensor, in return for a 10% royalty.

Exhibit 19 – Breakdown of sum-of-the-parts, rNPV-based valuation model

Product	Status	Indication	Launch	Peak sales (US$m)	NPV*(US$m)	Likelihood of approval	rNPV (A$)
CYP-001	Phase 2	aGvHD (Japan)	2023	119	30	70%	27,338,722
CYP-001	Phase 2	aGvHD (US & Europe)	2026	916	149	17%	32,510,666
CYP-004	Phase 3	Knee Osteoarthritis	2026	1599	307	50%	196,618,467
CYP-001	Phase 1/2	Respiratory Failure	2026	1228	197	17%	43,013,720
CYP-002	Phase 2	Critical Limb Ischemia	2026	1355	218	17%	47,565,202
TBD	Phase 1/2	Diabetic Foot Ulcers	2026	1115	154	17%	33,618,328
						Net cash (31 March 2021) (A$)	28,230,000
						Shares outstanding	138,564,299
						rNPV/share (A$)	2.95

Source: MST Access. * Assumes 10% royalty for all indications

Stem Cell therapy is evolving rapidly, and fast approaching a tipping point given the increased confidence in the quality and consistency of product being developed by companies such as Cynata. Exhibit 20 highlights several recent licensing deals relevant to Cynata's investment case.

Exhibit 20 – Recent licensing deals most relevant to Cynata

Date	Licensor	Licensee	Status	Indication(s)	Pharmacological class/target	Upfront (US$m	Milestones (US$m)
1-Jun-21	Novo Nordisk	Heartseed Inc	Pre-clinical	Cardiovascular Disease	iPSC derived Cardiomyocytes	55	598
17-May-21	BlueRock Therapeutics	FUJIFILM Cellular Dynamics/Opsis Therapeutics	Pre-clinical	Ocular Diseases (AML, IRD)	iPSCs	30 to 40	Undisclosed milestone, Low double digit royalties
20-Nov-20	Novartis	Mesoblast	Phase 3	Acute Respiratory Disease (ARDS) associated with COVID-19	Allogeneic MSCs	25	Plus 25m
7-Oct-20	Citius Pharmaceuticals	Novellus Therapeutics	Pre-clinical	Acute Respiratory Disease (ARDS) associated with COVID-19	iPSC derived MSCs (using mRNA technology)	5	51m in milestones, low double digit royalties
11-Aug-20	Kyocera Corporation	Regeneus	Phase 1	Knee Osteoarthritis (KO)	Allogeneic MSCs	13	14m in in regulatory and development milestone payments

Source: Fiercebiotech, Biospace, company data.

[9] Clinical Development Success Rates 2006-2015: BIO Industry Analysis (BIO, Biomedtracker, Amplion)

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Exhibit 21 – Valuation - key assumptions

Asset/indication	Metrics	Assumptions
CYP-001		
aGvHD (Japan)	Target population	Assuming 3,500 allogeneic HSCTs (bone marrow transplants) based on data from Japan Marrow Donor Program, the Japan Cord Blood Bank Network and the Asia Blood and Marrow Transplant Registry.
	Pricing	US$160,000
	Trial timelines	Assumes Phase 2 data meets contional approval with subsequent launch in 2023
CYP-001		
aGvHD (US & Europe)	Target population	Assuming 20,000 allogeneic HSCTs in Europe and 9,500 in the US with 50% of recipients developing aGvHD, of which 50% will present as steroid refractory.
	Pricing	US$200,000
	Trial timelines	Assumes Phase 3 commences in 2023 with subsequent FDA approval and launch in 2026
CYP-004		
Knee Osteoarthritis	Target population	Based on CDC data of 32.5m adults have OA in the US. According to the Lancet, the global prevalence of KO is 14%–18%.
	Pricing	US$5,000
	Trial timelines	Assumes FDA approval and launch in 2026
CYP-001		
Respiratory Failure	Target population	Assuming ARDS accounts for 10% of all ICU admissions, and ~25% of patients require mechanical ventilation. According to the ARDS Foundation, about 150,000 cases of ARDS are reported per year in the US.
	Pricing	US$40,000 - based on 10 days in ICU @ US$4K per day
	Trial timelines	Assumes FDA approval and launch in 2026
CYP-002		
Critical Limb Ischemia	Target population	Assuming 8 to 10 million Americans have arterial occlusive disease, leading to approximately 500–1,000 new cases of chronic limb ischemia per million people per year.
	Pricing	US$76,000 - based on proxy comparable in crohn's disease* (Alofisel by Takeda)
	Trial timelines	Assumes FDA approval and launch in 2026
TBD (MSC-seeded silicon dressing)		
Diabetic Foot Ulcers	Target population	Based on global prevalence of diabetic foot ulcers in diabetic patients varies from 3% in Oceania to 13% in North America, with a global average of 6.4%.
	Pricing	US$3,718
	Trial timelines	Assumes FDA approval and launch in 2026

Source: MST Access. *Www. medcitynews.com/2019/04/report-takeda-adopts-value-based-pricing-for-crohns-stem-cell-therapy-in-europe

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Sensitivities and Risks

Cynata Therapeutics is subject to all the risks typically associated with biotech company drug development, including the possibility of unfavourable outcomes in clinical trials, regulatory decisions, success of competitors, financing, and commercial decisions by partners or potential partners. In addition, key stock-specific sensitivities include:

Partnerships

Cynata's stated commercial strategy relies heavily on identifying and maintaining partnerships with other companies that can advance cell therapy products in key markets. Notwithstanding Cynata's alliance with Fujifilm in Japan, there is no guarantee that suitable partners will be found in other markets. Further, as a licensee of its core technology, the company could lose ownership rights should the licensor revoke rights or lose a claim of intellectual property infringement by a third party.

Technology and product development

The potential safety risks associated with MSC-based therapeutics, and iPSC-derived MSCs such as Cynata's are not fully understood. This may require further extensive and costly clinical trials to be conducted to address concerns from the FDA or other regulatory authorities. Cell therapies are subject to abnormal cell formations including malignant cell transformations and teratomas.

Funding risk

Cynata's currently solid cash position should be adequate to meet near-term goals given the prioritisation of clinical programs and strategic partnerships established to date. However, cost of trials and operational expenses may overrun estimates and require additional capital to be raised.

Regulatory

The regulatory approval pathway relating to stem cell therapies is still evolving. As knowledge grows of the mechanisms of action underpinning regenerative medicines, regulatory agencies are becoming more comfortable with assessing regulatory applications. Currently, the only stem cell products that are FDA-approved for use in the United States consist of blood-forming stem cells (also known as hematopoietic progenitor cells) that are derived from umbilical cord blood. As such and given the lack of established precedent for an iPSC-cell based therapeutic, the process associated for eventual registration may take longer than anticipated and may delay or prevent full commercialisation of any product based on Cynata's Cymerus™ technology.

Intellectual property

Wisconsin Alumni Research Foundation, or WARF, is the holder of the intellectual property. As a licensee of the intellectual property comprising Cynata's Cymerus™ technology, the company is still subject to any claims of patent infringement on other third-party technologies.

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Board and Management

Expertise and experience across the management team appear well suited to advancing Cynata's product development programs.

Dr Geoff Brooke (Chairman): Dr Brooke co-founded GBS Venture Partners in 1996 and has more than 30 years' venture capital experience. He was formerly President of Medvest Inc., a US-based early-stage venture capital group he founded with Johnson & Johnson. Dr Brooke's experience includes company formation and acquisitions as well as public listings on the NYSE, NASDAQ and ASX exchanges. He is a non-executive director of Acrux Limited (ASX: ACR) and Chairman of Actinogen Medical Limited (ASX: ACW) and has been a founder, executive and director of private and public companies. From 2009 until 2015, Dr Brooke was an independent director of the Victoria Workcover Authority. Dr Brooke holds a Bachelor of Medicine/Surgery from Melbourne University and a Master of Business Administration from IMEDE (now IMD) in Switzerland.

Dr Ross Macdonald (CEO & Director): Dr Macdonald has over 33 years' experience and a track record of success in pharmaceutical and biotechnology businesses. His career history includes positions as Vice President of Business Development for Sinclair Pharmaceuticals Ltd (now Sinclair Pharma plc), a UK-based specialty pharmaceuticals company, and Vice President, Corporate Development for Stiefel Laboratories Inc, the largest independent dermatology company in the world which was acquired by GlaxoSmithKline in 2009 for £2.25b. Dr Macdonald has also served as CEO of Living Cell Technologies Ltd, Vice President of Business Development of Connetics Corporation and Vice President of Research and Development of F H Faulding & Co Ltd. Dr Macdonald currently serves as a member of the Investment Committee of UniSeed Management Pty Ltd.

Dr Stewart Washer (Non-Executive Director): Dr Washer has over 27 years of CEO and board experience in medical technology and biotech companies. He is the Chairman of Emerald Clinics Ltd (ASX: EMD), Orthocell Ltd (ASX: OCC) and a Director of Botanix Pharmaceuticals Ltd (ASX: BOT). Dr Washer was previously a Director of Zelira Therapeutics Ltd (formerly Zelda Therapeutics Ltd) (ASX: ZLD) and AusBiotech and a Senator with Murdoch University.

Dr Paul Wotton (Non-Executive Director): Dr Wotton is the Chief Executive Officer of Obsidian Therapeutics, a leading synthetic biology company based in Cambridge, Massachusetts. Prior to this, he was the Founding President and CEO of Sigilon Inc. He was previously President and CEO of Ocata Therapeutics Inc. (NASDAQ: OCAT) guiding the company through a take-over by Astellas Pharma Inc., in a US$379m all-cash transaction. Dr Wotton is a member of the Board and Governance Committee of Vericel Corporation, a US company developing autologous cellular therapies and a member of the board at PaxMedica where he is Chairman of the Compensation Committee. Dr Wotton received his PhD in pharmaceutical sciences from the University of Nottingham.

Dr Darryl Maher (Non-Executive Director): Dr Maher adds global biopharmaceutical and commercialisation capability to the Cynata board, with over 23 years' experience with CSL Limited. CSL is one of the world's most successful developers of biologic pharmaceutical products and has a market capitalisation of ~A$130 billion. Dr Maher has had a long successful career in pharmaceutical product development, most recently as the former Vice President of R&D and Medical Affairs at CSL Behring Australia where he was responsible for the development of multiple successful drug products from initiation through to clinical development and ultimately to commercialisation. Dr Maher undertook medical training, qualified as a specialist haematologist and completed a PhD before commencing his career in the pharmaceutical industry.

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Appendix – Shareholder Register and Institutional Support

Exhibit 22 – Top 20 shareholders

Ordinary Shareholders	Number	Percentage
HSBC Custody Nominees (Australia) Limited	13,109,743	11.19%
Fujifilm Corporation	8,088,403	6.92%
BNP Paribas Nominees Pty Ltd	4,192,431	3.58%
J P Morgan Nominees Australia Limited	3,754,341	3.21%
Citicorp Nominees Pty Limited	2,958,639	2.53%
John W King Nominees Pty Ltd	2,373,596	2.03%
National Nominees Limited	2,217,794	1.89%
Mal Washer Nominees Pty Ltd	2,020,000	1.72%
Dr Ross Alexander Macdonald	2,000,000	1.71%
Brispot Nominees Pty Ltd	1,610,211	1.37%
Helium Management Pty Ltd	1,360,366	1.16%
Dr Maksym Vodyanyk	1,191,658	1.02%
Mr Jon Nicolai Bjarnason & Mrs Rina Eghoje Bjarnason	825,000	0.70%
Riversdale Capital Funding Pty Ltd	811,621	0.69%
Ms Kyoko Yukawa	800,000	0.68%
Tenbagga Resources Fund Pty Ltd	771,847	0.66%
CM Cook Superannuation Pty Ltd	700,000	0.60%
Neweconomy Com AU Nominees Pty Limited	682,781	0.58%
BNP Paribas Noms Pty Ltd	674,489	0.58%
Crosswind Trustee Company Limited	600,000	0.51%
Total	**50,742,920**	**43.33%**

Source: Cynata company reports.

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