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INITIATION OF COVERAGE | PUBLISHED ON 06 NOVEMBER 2024

CYP: Unlimited Cells, Unlimited Possibilities

CYP | CYNATA THERAPEUTICS LTD | HEALTHCARE | BIOTECHNOLOGY

PRICE	TARGET PRICE	RECOMMENDATION
0.22/sh	**0.75/sh**	**SPECULATIVE BUY**

Initiation of Coverage

Cynata Therapeutics (CYP) is a clinical-stage biotechnology company developing novel cell therapies in the field of regenerative medicines, with an initial rare disease focus.

The Company's unique patented Cymerus technology looks to revolutionise the development of mesenchymal stem cells (MSCs), a cell therapy with huge potential in various diseases, by overcoming the significant challenges faced by the sector to date.

Unlike conventional manufacturing methods that rely on an ongoing supply of donor cells and extensive cell expansion – leading to variable product consistency and potency, alongside scalability issues – Cymerus uses induced pluripotent stem cells (iPSCs) to produce a virtually unlimited, consistent and potent supply of MSCs, from a single donor.

The company's lead asset, CYP-001, is targeting acute graft versus host disease (aGvHD), a rare disease with a significant unmet need, evident by the very high rates of mortality. Currently in a phase 2 clinical trial and supported by impressive early results, aGvHD presents a rapid pathway to market for CYP to validate its platform, potentially enabling larger billion-dollar market opportunities down the track.

Investment Case

- **Sector-Leading Efficacy & Safety -** In a phase 1 aGvHD trial, high-dose CYP-001 treated patients achieved an 85.7% day-28 overall response (vs 62% with standard of care). Remarkably, the 2-year survival rate was 60% among the overall group of CYP-001 treated patients (vs 38% at 18 months with standard of care). Moreover, CYP-001 has also demonstrated a better safety profile than the standard of care.
- **Billion-Dollar Market Opportunity** - We estimate there is a A$1.2 billion total addressable market (TAM) for CYP-001 in the treatment of aGvHD across the United States and Europe alone, based on approx. ~14k patients estimated to suffer from aGvHD. Comparable drugs sell for between US$108k to US$170k per annum.
- **Major Industry Catalyst Approaching** - Commercial interest in MSCs could surge if Mesoblast's RYONCIL secures FDA approval by January 7th 2025 for pediatric steroid-resistant aGvHD. With the FDA's acceptance of their resubmitted BLA, approval seems likely. Importantly, this approval does not compete with CYP-001.
- **Multiple Shots on Goal** - In parallel to aGvHD, CYP is advancing clinical trials in various other indications, with total end markets worth in excess of US$10 billion.

Price Target and Recommendation

We initiate with a Speculative Buy Recommendation and $0.75 Price Target

Our risked-NPV_{15} Valuation assumes CYP-001 is granted approval for aGvHD and captures 50% peak market share in the USA and Europe. This assumes CYP executes two US$125 million licensing deals, one for the USA and one for the EU. **Our fully unrisked valuation is $1.53 in acute GvHD alone.**

We do not ascribe any value for CYP-001 in the rest of the world, or for CYP's development pipeline (incl. diabetic foot ulcers, osteoarthritis or kidney transplantation). Some of these indications have end markets worth in excess of US$10 billion.

Catalysts

Phase 2 aGvHD Study Results - Late CY25/Phase 1 Diabetic Foot Ulcer Study Results - Late CY24 or Early CY25/Mesoblast FDA Outcome (Industry Catalyst) - Jan 7 2025

Analyst

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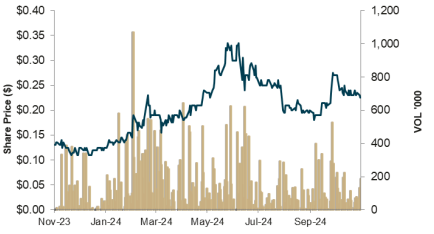
Share Price	**0.22**	**A$/sh**
Price Target	**0.75**	**A$/sh**
Risked Valuation	**0.75**	**A$/sh**
Unrisked Valuation	**1.53**	**A$/sh**
WACC	15%	%
TGR	2%	%
Shares on issue	185.6	m,dil
Market Cap	**40.8**	**A$m**
Enterprise Value	**35.6**	**A$m**
Debt (inc. leases)	0.0	A$m
Cash (Sep'Q)	4.3	A$m
Unpaid capital*	0.9	A$m
*in-the-money		

Key Metrics	**25F**	**26F**	**27F**
Revenue (A$m)	1.7	16.6	19.4
EBITDA (A$m)	-6.5	-17.9	-7.5
EBIT (A$m)	-6.7	-18.1	-7.7
NPAT (A$m)	-6.7	-18.1	-7.7
Gross CF (A$m)	-6.5	-17.9	-7.5
Capex (A$m)	0.0	0.0	0.0
Op. FCF (A$m)	-6.5	-16.5	-8.8
EPS (Ac)	-3.8	-10.1	-4.3
Revenue Growth	-0.4	8.5	0.2
PER (x)	na	na	na
EV/EBITDA (x)	na	na	na
EV/Revenue (x)	20.5	2.1	1.8
Net Cash	4.7	28.2	19.4

Performance



Source: IRESS

Contents

Income Statement	25F	26F	27F	28F
Milestone Payments	0.0	16.2	16.2	0.0
Royalty Income	0.0	0.0	0.0	0.0
Other (incl. R&D)	1.7	0.4	3.3	2.2
Revenue	**1.7**	**16.6**	**19.4**	**2.2**
(-) R&D	-4.6	-30.8	-23.1	-7.7
(-) SG&A	-3.6	-3.7	-3.8	-4.0
EBITDA	**-6.5**	**-17.9**	**-7.5**	**-9.5**
(-) D&A	-0.2	-0.2	-0.2	-0.2
EBIT	**-6.7**	**-18.1**	**-7.7**	**-9.6**
(-) Finance	0.0	0.0	0.0	0.0
(+/-) Other	0.0	0.0	0.0	0.0
PBT	**-6.7**	**-18.1**	**-7.7**	**-9.6**
(-) Tax	0.0	0.0	0.0	0.0
NPAT	**-6.7**	**-18.1**	**-7.7**	**-9.6**

Cash Flow Statement	25F	26F	27F	28F
NPAT	**-6.7**	**-18.1**	**-7.7**	**-9.6**
(+) D&A	0.2	0.2	0.2	0.2
(+) Non-cash expenses	0.0	0.0	0.0	0.0
(-) Leases	0.0	0.0	0.0	0.0
(+/-) Other	0.0	0.0	0.0	0.0
Gross Cash Flow	**-6.5**	**-17.9**	**-7.5**	**-9.5**
(-) Capital Expenditure	0.0	0.0	0.0	0.0
(-) Net Working Capital	0.0	1.4	-1.3	0.2
Operating Free Cash Flow	**-6.5**	**-16.5**	**-8.8**	**-9.2**
(-) Acquisition	0.0	0.0	0.0	0.0
(-) Dividend	0.0	0.0	0.0	0.0
(+) Disposal	0.0	0.0	0.0	0.0
(+) Equity Issue	5.0	40.0	0.0	0.0
(+/-) Other	0.0	0.0	0.0	0.0
Net Cash Flow	**-1.5**	**23.5**	**-8.8**	**-9.2**
BoP Net Cash / (Debt)	**6.2**	**4.7**	**28.2**	**19.4**
(+/-) Net Cash Flow	-1.5	23.5	-8.8	-9.2
(+/-) AASB16	0.0	0.0	0.0	0.0
EoP Net Cash / (Debt)	**4.7**	**28.2**	**19.4**	**10.2**

Balance Sheet	25F	26F	27F	28F
Cash	4.7	28.2	19.4	10.2
Receivables	0.1	2.0	2.4	0.3
Prepayments	0.2	0.2	0.2	0.2
Total Current Assets	**5.0**	**30.4**	**22.0**	**10.6**
Intangibles	1.6	1.4	1.2	1.1
Total Non Current Assets	**1.6**	**1.4**	**1.2**	**1.1**
Total Assets	**6.6**	**31.8**	**23.2**	**11.7**
Payables	1.0	4.3	3.3	1.4
Provisions	0.2	0.2	0.2	0.2
Total Current Liabilities	**1.2**	**4.5**	**3.5**	**1.7**
Total Liabilities	**1.2**	**4.5**	**3.5**	**1.7**
Net Assets	**5.5**	**27.4**	**19.7**	**10.0**
Issued Capital	86.6	126.6	126.6	126.6
Reserves	7.9	7.9	7.9	7.9
Retained Earnings	-89.1	-107.2	-114.9	-124.5
Total Equity	**5.5**	**27.4**	**19.7**	**10.0**

Performance Ratios	25F	26F	27F	28F
Growth				
Revenue Growth (%)	-36%	853%	17%	-89%
EBITDA Growth (%)	-31%	176%	-58%	26%
EBIT Growth (%)	-31%	169%	-58%	25%
NPAT Growth (%)	-31%	169%	-58%	25%
Margin				
EBITDA Margin (%)	-373%	-108%	-39%	-436%
EBIT Margin (%)	-387%	-109%	-40%	-443%
PBT Margin (%)	-387%	-109%	-40%	-443%
NPAT Margin (%)	-387%	-109%	-40%	-443%
Effective Tax Rate (%)	0%	0%	0%	0%
Liquidity				
Capex/depreciation (x)	0	0	0	0
Current ratio (x)	4.3	6.8	6.2	6.4
Quick ratio (x)	5.1	7.1	6.6	7.3
Receivable days	23.7	45.0	45.0	45.0
Payable days	42.1	45.0	45.0	45.0
Risk Measures				
Dividend Cover (x)	na	na	na	na
Payout ratio (%)	0%	0%	0%	0%
Net interest cover (x)	na	na	na	na
Net debt/equity (%)	-86%	-103%	-99%	-101%
Returns				
ROIC (%)	na	na	na	na
ROA (%)	na	na	na	na
ROE (%)	na	na	na	na

Share Data/Valuation	25F	26F	27F	28F
Share Data				
Issued shares (m)	179.6	179.6	179.6	179.6
Weighted ave shares (m)	179.6	179.6	179.6	179.6
Fully diluted shares (m)	214.3	214.3	214.3	214.3
Basic EPS (c)	-3.8	-10.1	-4.3	-5.4
YoY change (%)	na	na	na	na
Fully diluted EPS (c)	-3.1	-8.5	-3.6	-4.5
YoY change (%)	na	na	na	na
Fully dil norm EPS (c)	-3.1	-8.5	-3.6	-4.5
YoY change (%)	na	na	na	na
Dividend/share (c)	0.0	0.0	0.0	0.0
Franking (%)	na	na	na	na
Gross cash flow/share (c)	-3.6	-10.0	-4.2	-5.3
NBV/share (c)	3.0	15.2	10.9	5.6
NTA/Share (c)	2.2	14.5	10.3	5.0
Share Data				
PER (Basic) (x)	na	na	na	na
PER (Fully diluted) (x)	na	na	na	na
PER (Fully dil, norm) (x)	na	na	na	na
P/CFPS (x)	na	na	na	na
Price/NBV (x)	7.2	1.4	2.0	3.9
Price/NTA (x)	10.2	1.5	2.1	4.4
Dividend Yield (%)	0.0	0.0	0.0	0.0
EV/EBITDA (x)	na	na	na	na
EV/EBIT (x)	na	na	na	na
EV/Revenue (x)	20.5	2.1	1.8	16.4

Valuation and Price Target

We initiate coverage with a Speculative Buy Recommendation and a $0.75 Valuation and Price Target

Our Valuation assumes CYP's lead asset, CYP-001, is granted approval in the United States and Europe as a treatment for acute GvHD in CY 2029 and is subsequently commercialised in both regions under an out-licensing model.

Our Valuation is derived using a sum of the parts (SOTP) risked net present Valuation (rNPV). (Figure 1).

Figure 1: Sum of the Parts (SOTP) Valuation

SOTP Valuation (Fully Diluted)	NPV15	NPV15	Risking (r)	rNPV15	rNPV15
	(A$m)	(A$/sh)	(%)	(A$m)	(A$/sh)
USA (aGvHD)	138.8	0.64	50%	69.9	0.32
Europe (aGvHD)	199.0	0.92	50%	100.3	0.47
Rest of World (aGvHD)	0.0	0.00	100%	0.0	0.00
Other Assets/Indications	0.0	0.00	100%	0.0	0.00
Corporate	-27.3	-0.13	100%	-27.3	-0.13
Enterprise Value	**310.6**	**1.44**		**142.9**	**0.66**
(-) Debt (excl. leases)	0.0	0.00	100%	0.0	0.00
(+) Cash	4.3	0.02	100%	4.3	0.02
(+) unpaid capital	13.8	0.06	100%	13.8	0.06
Equity Value	**328.6**	**1.53**		**161.0**	**0.75**
Upside		594%			240%

Source: EH analysis, 0.66 AUD/USD Fx, fully diluted for all options outstanding

Our fully unrisked valuation is $1.53 in acute GvHD.

Our Valuation is derived using a conservative 15% discount rate and is risk adjusted (r) based on the average probability of success from phase 2 to approval for non-oncology orphan drugs (~50%, Figure 2). Our Valuation includes a terminal value and is fully diluted for any options outstanding.

Figure 2: Non-oncology Orphan Drug Phase Success Rates

		Phase 1	Phase 2	Phase 3	NDA Approval
Orphan non-oncology					
Phase Success Rate	%	88%	81%	73%	85%
Phase Likelihood of Approval (LOA)	%	45%	50%	62%	85%

Source: Hay et al, January 2014

Our Valuation assumes CYP executes two US$125m licensing deals (including a $15m upfront) for CYP-001 in acute GvHD, one for the United States and one for Europe.

We note there is potentially for a much larger deal, considering that Eli Lilly (NYSE: LLY) paid an upfront payment of US$35m (in addition to milestones and royalties) in a licensing deal with Incyte (NASDAQ: INCY) for the ex-USA rights to Ruxolitinib in GvHD.

Key assumptions driving our valuation in acute GvHD include:

- Est 6.9k combined target steroid resistant acute GvHD patient population across both US and EU.
- 50% peak market share.
- US$150k/US$100k pricing in United States and EU respectively (comparable drugs sell for between US$108-170k pa).

We provided a full breakdown of our forecasts of CYP-001 in acute GvHD in the United States and Europe in Figure 58 and Figure 59 respectively, with supporting analysis on the total addressable market for acute GvHD (including sizing and pricing) on page 43.

We do not ascribe any Value for CYP-001 in acute GvHD in the rest of the world (RoW), including Japan and China. Further licensing deals in this indication present upside to our valuation.

Additionally, we do not ascribe any value for CYP's development pipeline, which includes CYP-006TK in diabetic foot ulcers, CYP-004 in osteoarthritis (investigator led), and CYP-001 in kidney transplantation (investigator led). This pipeline includes total end markets worth in excess of US$10 billion per annum and clearly represents potential upside to our valuation.

Ultimately, we believe acute GvHD will present a rapid pathway to market for CYP to validate its Cymerus platform, potentially enabling larger multi-billion-dollar market opportunities down the track. MSCs have broad therapeutic potential in a number of indications (Figure 18).

The risks surrounding our assumptions further drive our Speculative Buy recommendation.

Valuation Sensitivity

We have sensitised a handful of key inputs behind our $0.75 Valuation.

Figure 3: Discount Rate vs Risk Adjustment (r)

Risking (r, %) \ Discount Rate (%)	7.5%	10.0%	12.5%	15.0%	17.5%
40.0%	1.87	1.16	0.80	0.59	0.45
50.0%	2.39	1.47	1.01	0.75	0.57
60.0%	2.90	1.79	1.23	0.90	0.69
70.0%	3.42	2.11	1.45	1.06	0.81
80.0%	3.93	2.42	1.67	1.22	0.93

Source: EH analysis

Figure 4: Discount Rate vs Terminal Growth Rate (TGR)

Terminal Growth Rate (%) \ Discount Rate (%)	7.5%	10.0%	12.5%	15.0%	17.5%
0.0%	2.01	1.34	0.96	0.72	0.56
1.0%	2.18	1.40	0.99	0.73	0.57
2.0%	2.40	1.48	1.02	0.75	0.58
3.0%	2.73	1.59	1.06	0.77	0.59
4.0%	3.24	1.72	1.12	0.79	0.60

Source: EH analysis

Figure 5: USA Pricing vs Peak USA Market Share

Peak Market Share (%) \ USA Pricing (US$'000s pa)	100.0	125.0	150.0	200.0	250.0
10%	0.50	0.50	0.51	0.56	0.55
30%	0.57	0.60	0.62	0.69	0.75
50%	0.73	0.70	0.75	0.84	0.93
70%	0.73	0.80	0.86	0.98	1.09
90%	0.80	0.88	0.96	1.11	1.26

Source: EH analysis

Figure 6: EU Pricing vs Peak EU Market Share

Peak Market Share (%) \ EU Pricing (US$'000s pa)	50.0	75.0	100.0	150.0	200.0
10%	0.36	0.38	0.40	0.45	0.49
30%	0.45	0.60	0.59	0.71	0.83
50%	0.54	0.65	0.75	0.94	1.13
70%	0.63	0.77	0.90	1.17	1.43
90%	0.71	0.88	1.05	1.39	1.73

Source: EH analysis

Figure 7: Est USA Acute GvHD Prevalence vs Peak USA Market Share

Peak Market Share (%) \ Estimated USA Acute GvHD Prevalence ('000s)	1.7	2.2	2.7	3.2	3.7
10%	0.50	0.51	0.52	0.54	0.55
30%	0.59	0.62	0.67	0.71	0.75
50%	0.68	0.75	0.82	0.87	0.93
70%	0.78	0.86	0.94	1.02	1.10
90%	0.86	0.96	1.07	1.17	1.28

Source: EH analysis

Figure 8: Est EU Acute GvHD Prevalence vs Peak EU Market Share

Peak Market Share (%) \ Estimated EU Acute GvHD Prevalence ('000s)	4.4	4.9	5.4	5.9	6.4
10%	0.43	0.40	0.42	0.42	0.43
30%	0.56	0.59	0.61	0.64	0.66
50%	0.71	0.75	0.79	0.83	0.87
70%	0.85	0.90	0.95	1.01	1.06
90%	0.98	1.05	1.12	1.19	1.26

Source: EH analysis

Stem Cell Related Mergers and Acquisitions (M&A)

In recent years there has been a number of stem cell related mergers and acquisitions, with some transactions valued as high as US$1bn.

Figure 9: Stem Cell Related Mergers and Acquisitions (M&A)

Year	Acquirer	Target	Transaction Value (US$M)	Description
2011	TiGenix	Cellerix	80	Allogeneic adipose-derived stem cell therapies
2014	NeoStem	California Stem Cell	124	Stem cell production technology
2015	AMAG Pharmaceuticals	Cord Blood Registry	700	Housed +600,000 preserved umbilical cord blood and tissue stem cell units
2015	FUJIFILM Holdings	Cellular Dynamics	307	Functioning human cells, including induced pluripotent stem cells (iPSCs)
2018	Astellas Pharma	Ocata Therapeutics	379	Human embryonic stem cells (hESC) and induced pluripotent stem cells (iPSCs)
2018	Takeda Pharmaceutical	TiGenix	632	Allogeneic adipose-derived stem cell therapies
2018	Astellas Pharma	Universal Cells	103	Stem cell therapies using genome editing
2019	Bayer	Blue Rock Therapeutics	1,000*	Cell therapies using induced pluripotent stem cells (iPSCs)
2019	Vertex Pharmaceuticals	Semma Therapeutics	950	Stem cell-based diabetes therapies
2021	Brooklyn ImmunoTherapeutics	Novellus Therapeutics	125	MSC therapies using mRNA-based cell reprogramming and gene editing
2024	Century Therapeutics	Clade Therapeutics	45	Stem cell therapies

*Source: EH analysis, company announcements, media articles; *including 40.8% pre-acquisition equity stake*

We note CYP has attracted significant commercial interest in the past

In 2017, the company entered into a strategic development and commercialisation agreement with Fujifilm corporation for its lead asset, CYP-001, in acute GvHD. As part of this agreement, Fujifilm was granted an option for the right to exercise an exclusive, worldwide license to market and sell CYP-001 in acute GvHD. If exercised, CYP would be eligible to receive up to $60m in milestone payments and double digit royalties on net sales.

Fujifilm additionally took at ~$4m strategic equity stake in CYP, which it still holds to this day.

Notably, this agreement was done on preclinical data alone, prior to the commencement of the phase 1 acute GvHD trial. Likely also explaining the relatively small deal size.

In July 2019, CYP announced it had received an indicative, non-binding and conditional $2.00 per share cash takeover from major Japanese conglomerate, Sumitomo Group. Which implied a ~$217 million equity value.

However, in August 2019, Fujifilm exercised its option for a worldwide license of CYP-001 in acute GvHD. We believe this outcome likely contributed to Sumitomo withdrawing its $2.00 takeover offer a few weeks later, as CYP-001 in aGvHD was the company's most advanced asset.

Further complicating matters, in 2021 during the COVID-19 pandemic, Fujifilm opted to restructure the agreement into a manufacturing agreement and return the rights for CYP-001 in acute GvHD back to CYP. We speculate Fujifilm made this move as it appeared to have strategically refocused to manufacturing, rather than therapy development, as evident by its acquisition of Cellular Dynamics.

Case Study – Upside Potential

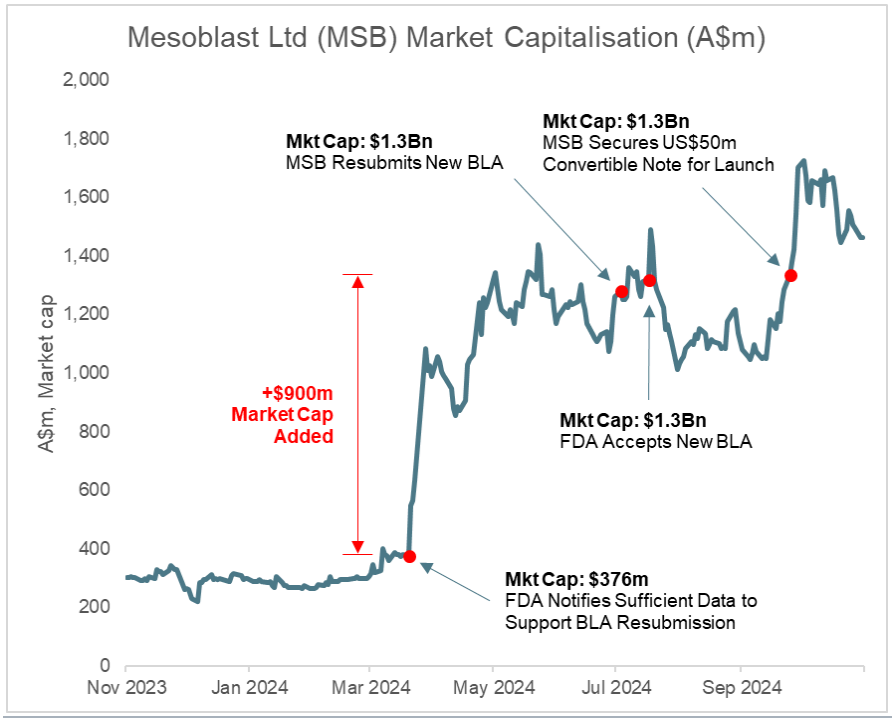
Mesoblast Ltd (ASX: MSB), a key ASX-listed peer operating in the MSC field, presents a compelling case study of the potential value upside in CYP.

MSB is developing conventionally manufactured, bone-marrow derived MSC therapies. Its lead product, RYONCIL (Remestemcel-L), is expected to be granted FDA-approval on or before January 7th 2025 as a treatment for paediatric steroid-resistant acute GvHD.

In October 2022, the FDA issued MSB a Complete Response Letter on RYONCIL's biological license application (BLA) recommending additional clinical studies. In a second Complete Response Letter in August 2023, the FDA again indicated additional clinical studies were required. However, in a surprise turnaround earlier this year, the FDA notified MSB it had sufficient data to support a resubmission of its RYONCIL BLA.

In the weeks following this major FDA announcement, MSB added more than $900 million in total market capitalisation – highlighting the implied value for acute GvHD.

Figure 10: Mesoblast Ltd (ASX: MSB) Market Capitalisation



Source: IRESS, Company announcements, EH analysis

As of the writing of this report, MSB had a ~$1.5 billion market cap. Moreover, even before this FDA announcement, it still had a ~$380 million market cap.

While we acknowledge MSB is clearly more advanced than CYP, it still highlights the significant potential value upside in developing novel MSC-based therapies.

In parallel, we anticipate that commercial activity in the MSC space could significantly increase if RYONCIL receives FDA approval in early 2025.

Importantly, we note that the potential approval of RYONCIL would not compete with CYP, as it would apply only to paediatric steroid-resistant acute GvHD—a small subset of acute GvHD estimated to number in the hundreds of patients. Furthermore, while the FDA may be open to approving RYONCIL for this ultra-rare condition due to the significant unmet need, we believe MSB will still face challenges in pursuing approval for both adult steroid-resistant acute GvHD as well as larger indications.

Key Risks

We outline key risks to our investment case below:

- **Clinical Development** – The success of the phase 2 clinical trial of CYP's lead asset, CYP-001, for the treatment of acute graft vs host disease (aGvHD) is key to our investment case. There are also risks in the development of CYP's other programs, including Diabetic Foot Ulcers (DFU), Osteoarthritis (OA) and Kidney Transplantation.
- **Regulatory** – Securing regulatory approval in key jurisdictions, including the United States and Europe, is required to commercialise CYP-001 as a treatment for aGvHD.
- **Intellectual Property** – CYP maintains an extensive intellectual property portfolio, loss or issues surrounding these patents could impact the business. On balance, due to the nature of biologics, they don't face the same risks around 'generic' entrances as small molecule drugs.
- **Key Personnel** – The company has a number of experienced personnel. Loss of any key individuals could impact the business.
- **Commercialisation** – The future commercial success of CYP-001 in aGvHD is key to our investment case.
- **Competition** – While we believe CYP has one of the most advanced and promising therapies in development for aGvHD, the development of competing drugs is a potential risk to the business. We have evaluated key competitors in this report.
- **Funding** – CYP is currently cash flow negative and will likely require additional capital to fund the development of CYP-001 and its other programs. There remain the usual risks around timing of any future funding requirements.

Company Overview

CYP is a clinical-stage biotechnology company developing novel cell therapies in the area of regenerative medicines, with an initial rare disease focus.

Figure 11: Company logo

Source: Company website

Founded in 2011, CYP has developed a unique manufacturing platform, Cymerus, which looks to revolutionise the field of mesenchymal stem cells (MSCs).

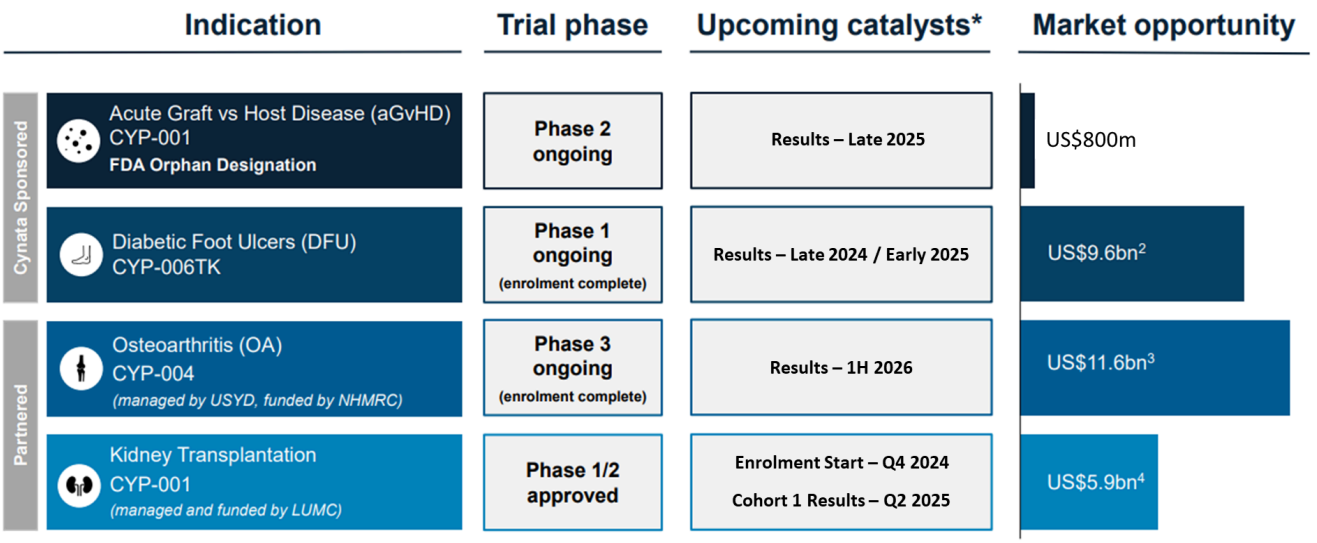
Mesenchymal stem (or stromal) cells are a type of adult stem cell with huge therapeutic potential. Despite promising research on its application in a number of diseases, there has been considerable challenges in producing a consistent and potent product at scale.

Current manufacturing methods rely on ongoing donors and subsequent cell expansion, which creates considerable challenges. As of this report, there were no FDA approved MSC therapies on the market.

CYP's technology overcomes these issues by utilising induced Pluripotent Stem Cell (iPSC), which enables the production of a near unlimited amount of MSCs from a single donor, without losing potency or facing issues of consistency. CYP is the only company to have done clinical trials of iPSC-derived MSCs.

CYP's lead program is in Acute Graft vs Host Disease (aGvHD), a rare inflammatory disease with high rates of mortality and a overall significant unmet need. In parallel, the company is pursuing various other indications in diseases with large unmet needs (Figure 12), some of these are investigator led studies with little to no capital outlay required by CYP.

Figure 12: Clinical Development Pipeline

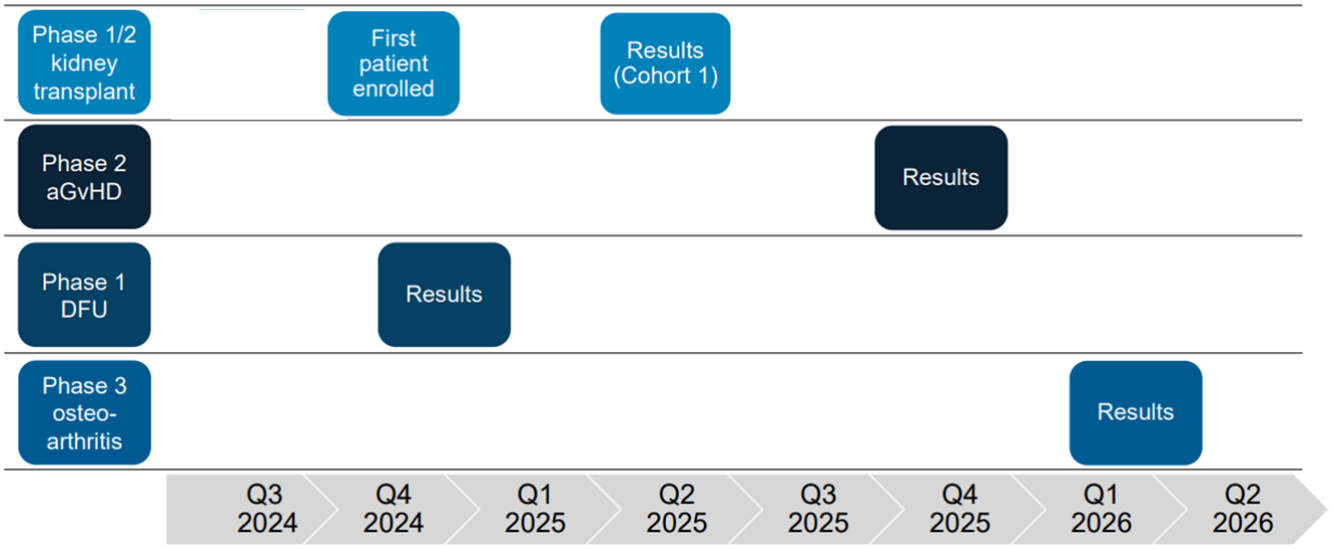


Source: Company presentation, september quarterly result, EH analysis

Further, the company has a trove of preclinical data showing the utility of its Cymerus platform in a number of disease models including: critical limb ischemia, idiopathic pulmonary fibrosis, asthma, heart attack, sepsis, acute respiratory distress syndrome (ARDS) and cytokine release syndrome.

The company has a number of data readouts over the next 6-18 months from various programs, some of which we believe could catalyse commercial partnering activity.

Figure 13: Upcoming catalysts



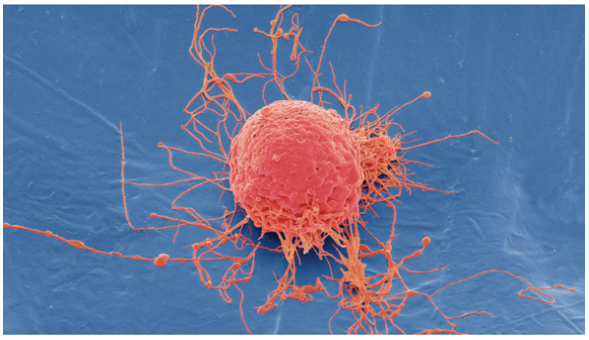
Source: Company presentation

Mesenchymal Stem Cells (MSCs)

Overview

Mesenchymal Stem Cells (MSCs), also known as Mesenchymal Stromal Cells, are a type of adult stem cell found in various body tissues (e.g. bone marrow) with significant therapeutic potential in a number of diseases (Figure 14).

Figure 14: Scanning Electron Micrograph of a Single Mesenchymal Stem Cell



Source: Clear up this stem-cell mess

These cells possess broad and complex immunomodulating and trophic (regenerative) properties, driven by their production of various growth factors and cytokines – which has earned them the nickname “drug factories”.

Initially, research of MSCs focused on their ability to differentiate into multiple mesenchymal lineages (e.g. cartilage, bone and fat cells) – which is where they get their stem cell nomenclature. However, this classification is increasingly debated, with new research suggesting MSC differentiation only occurs under certain conditions in vitro and not after implantation in vivo. Despite this debate, MSC differentiation is not particularly relevant to CYP’s therapeutic applications.

Despite its significant therapeutic potential, the successful development and commercialisation of MSC’s has faced significant challenges – most of which leads back to manufacturing, as we will discuss in this research.

There are currently no FDA-approved MSC therapies. However, the Biologics License Application (BLA) for bone marrow-derived MSC therapy, Remestemcel-L (Mesoblast, MSB: ASX), is currently under review pending an expected approval decision in early 2025 as a treatment for paediatric steroid-resistant acute graft vs host disease (Sr-aGvHD). We believe this would represent a major catalyst for the sector.

Outside the United States, there are a handful of countries with approved MSC therapies (Figure 15), including Japan which introduced a supportive regulatory pathway for cell therapies.

Figure 15: Ex-USA approved MSC Therapies

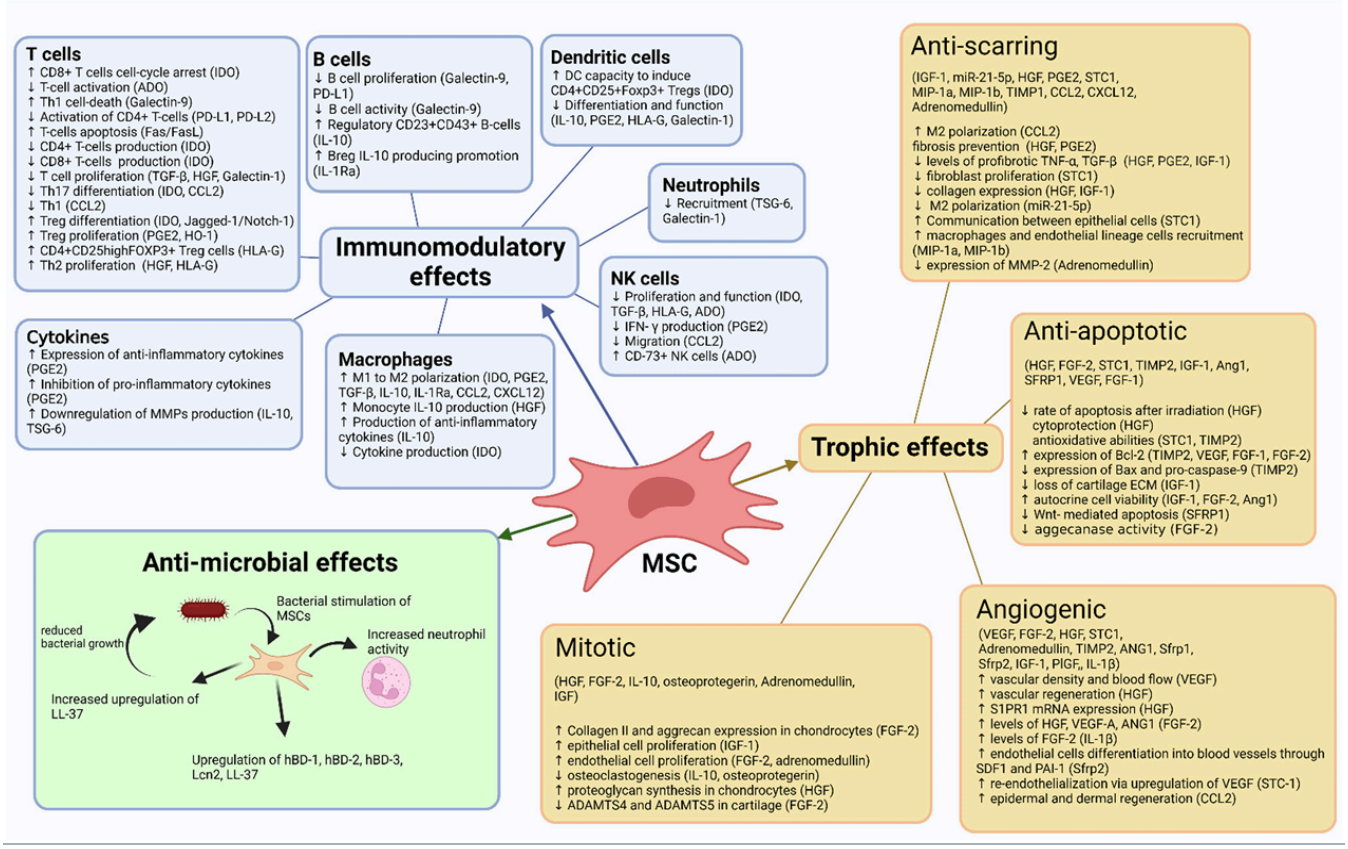
Name	MSC type	Indication	Country of approval (year)	Company
Alofisel	Human AT-MSC	Complex perianal fistulas in CD	Europe (2018)	TiGenix NV/Takeda
Prochymal (remestemcel-L)	Human BM-MSC	GvHD	Canada (2012), New Zealand (2012)	Osiris Therapeutics Inc./Mesoblast Ltd.
Temcell HS Inj	Human BM-MSC	GvHD	Japan (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	Amyotrophic 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, *list not exhaustive*

Multifaceted Mechanism of Action

Subject to the environment MSCs are located in, the cells secrete a variety of bioactive molecules which have immunomodulating, trophic and even antimicrobial effects. A summary of the complicated cascade of factors involved is shown below (Figure 16).

Figure 16: Mesenchymal Stem Cells Mechanisms of Action



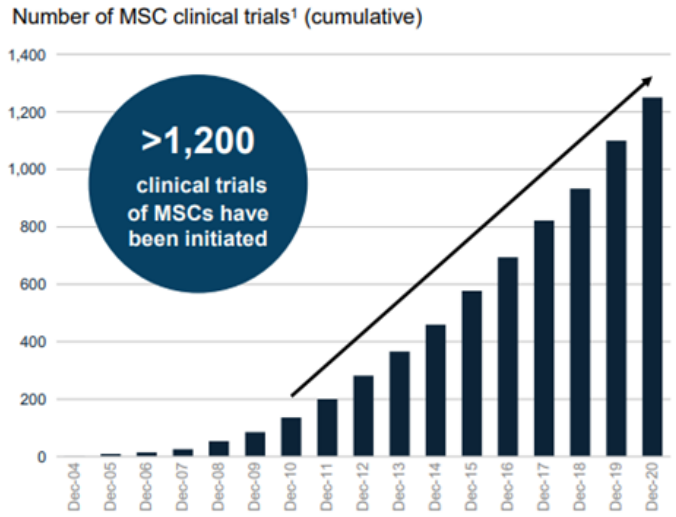
Source: Molnar V, Pavelić E, Vrdoljak K, Čemerin M, Klarić E, Matišić V, Bjelica R, Brlek P, Kovačić I, Tremolada C, Primorac D. (2020)

Excellent Safety Profile

MSC's have been extensively studied over the last three decades and have exhibited an excellent safety profile in that time.

The scientific literature estimates over 10,000 patients have been administered MSC's in a clinical trial setting. Moreover, the same literature states between 2011-18, there were an estimated 1,000 clinical trials planned targeting to enrol close to ~50,000 patients globally.

Figure 17: Number of MSC Trials, Cumulative



Source: Company presentation

Similarly, CYP's own MSCs have demonstrated an excellent safety and tolerability profile both in preclinical and clinical trials.

Key to this safety profile is that MSC's do not elicit an immune reaction, as they lack human leukocyte antigen (HLA) class II expression, which enables allogeneic (donor) administration.

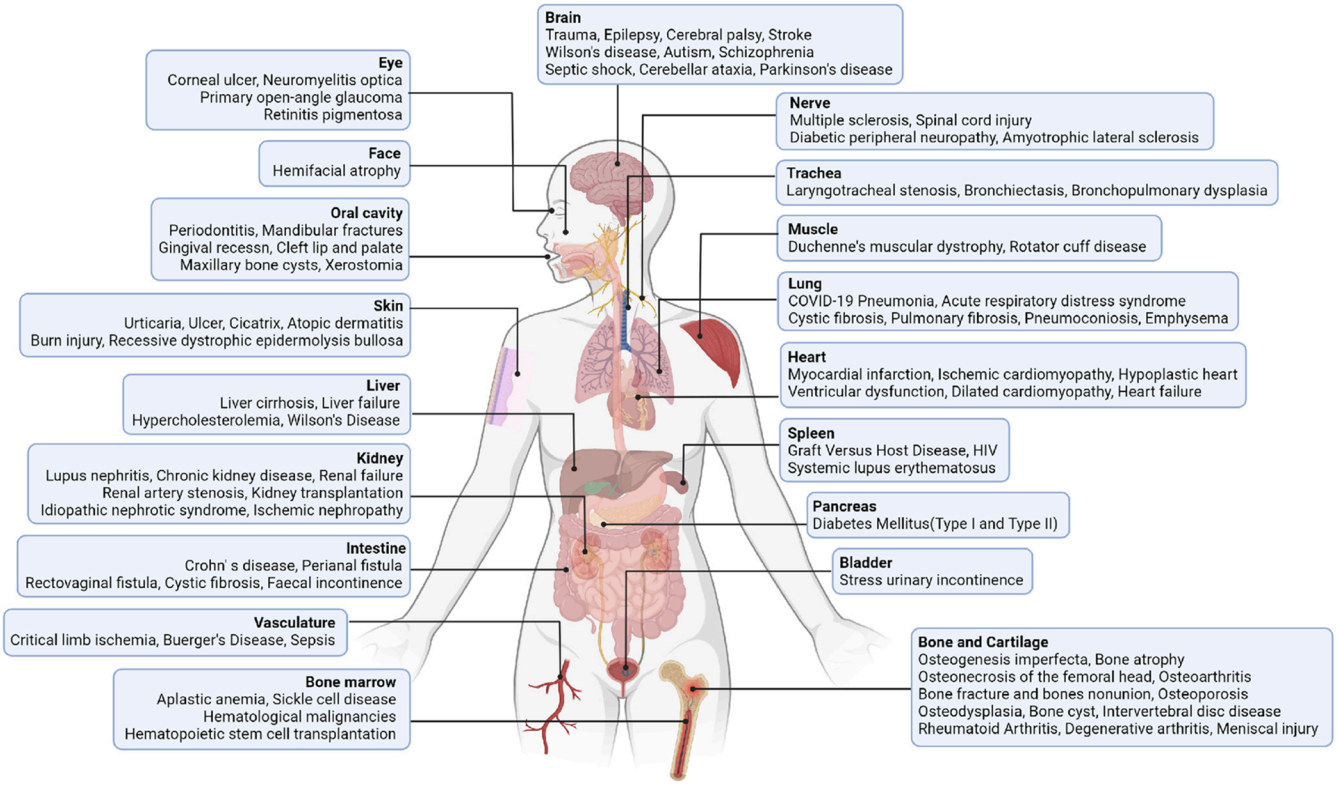
MSC's don't rely upon engraftment (i.e. becoming incorporated into the host) – as a result, once the cells exert their effect (through the release of bioactive molecules, see Figure 16), they are then eliminated from the body in a relatively short period of time.

Furthermore, as MSC's function by regulating the immune system, i.e. immunomodulation, compared to broad and blunt immune suppression, they aren't associated with harsh adverse effects, such as increased risk of infection.

Broad Therapeutic Potential

The multifaceted immunomodulatory and trophic properties of MSCs suggest these cells could have therapeutic application across a wide area of conditions, including those centred around inflammation, wound healing, infection, and degenerative diseases.

Figure 18: Diseases Evaluated with MSCs in Clinical Trials



Source: Han, Y., Yang, J., Fang, J. et al. (2022)

CYP has focused its efforts in initiating clinical programs in indications where there is a high unmet need and a clear pathway to market.

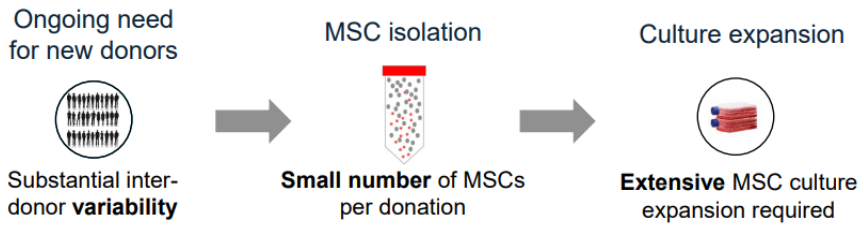
Existing MSC Challenges: Manufacturing

MSC's present a promising new therapy, particularly for immune and inflammatory mediated conditions (Figure 18), however, their clinical application remains restricted by significant manufacturing challenges. As of the writing of this report, there remains no FDA approved MSC therapy on the market.

There have been over 1,000 clinical trials involving MSC's in the last three decades. While MSC's have shown some very impressive results across a number of smaller / earlier stage studies, their translation into larger scale and later stage trials remains elusive. While this remains a debated area, there seems to be broader agreement around the significant limitations with existing methods of manufacturing MSC's which are thought to contribute to this translation issue.

The conventional process of manufacturing MSC's usually relies on first sourcing MSC's from a donor (such as bone marrow), isolating the MSC's, and subsequently expanding them in culture to produce MSCs at scale (Figure 19).

Figure 19: Conventional MSC Manufacturing Process



Source: Company presentation

However, there are a few fundamental issues with this process:

1. Donors yield a relatively small number of MSC's.
2. There is considerable inter-donor variability; and
3. There are limits to the in-culture expansion capacity of MSC's.

As we discuss in the following section, we believe CYP's Cymerus iPSC-derived MSC manufacturing process overcomes these issues.

Ongoing Reliance on Donors

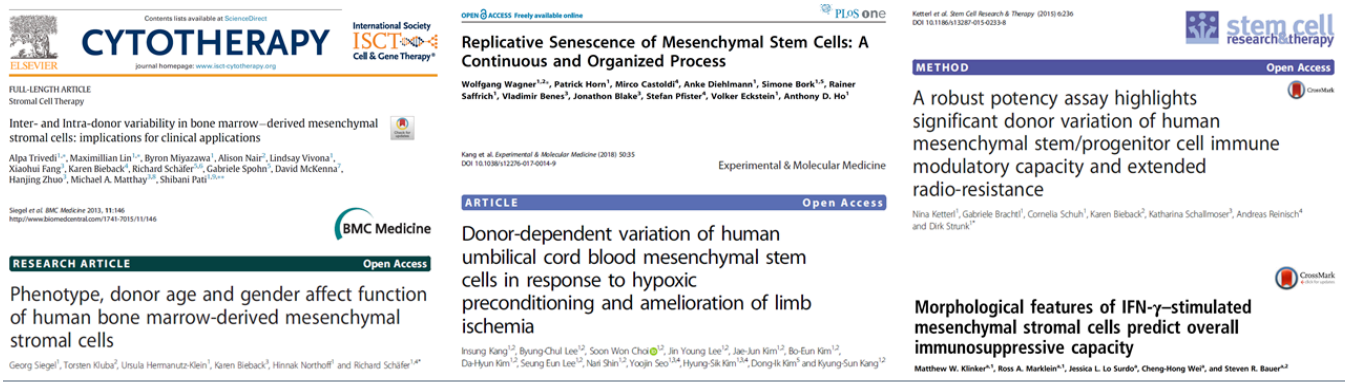
Conventional MSC manufacturing relies on an ongoing source of cells from donors, most of which is bone-marrow derived. This presents a considerable logistical hurdle in establishing commercial scale manufacturing, more so if the therapy is designed for larger indications.

This issue is further compounded by the inter-donor variability and the limitations of in-culture expansion of MSC's, as we discuss below. These factors highlight how conventional MSC manufacturing processes can ultimately require a very large number of donors.

Inter-donor Variability

Various studies (Figure 20) have shown considerable heterogeneity in MSC's from different donors, with variations observed in characteristics such as adipogenic potential and immunosuppressive capacity.

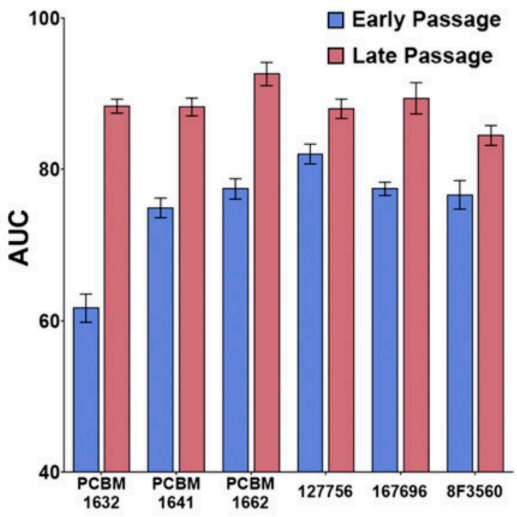
Figure 20: Publications Discussing Inter-donor MSC Variability



Source: EH analysis, Various publications

The diagram below (Figure 21) illustrates the variance in immunosuppressive capacity between different MSC lines and in-culture durations (early vs late passages), whereby a lower area under the curve (AUC) represents a higher immunosuppressive capacity.

Figure 21: MSC Immunosuppressive Capacity Between MSC Lines and In-culture Duration



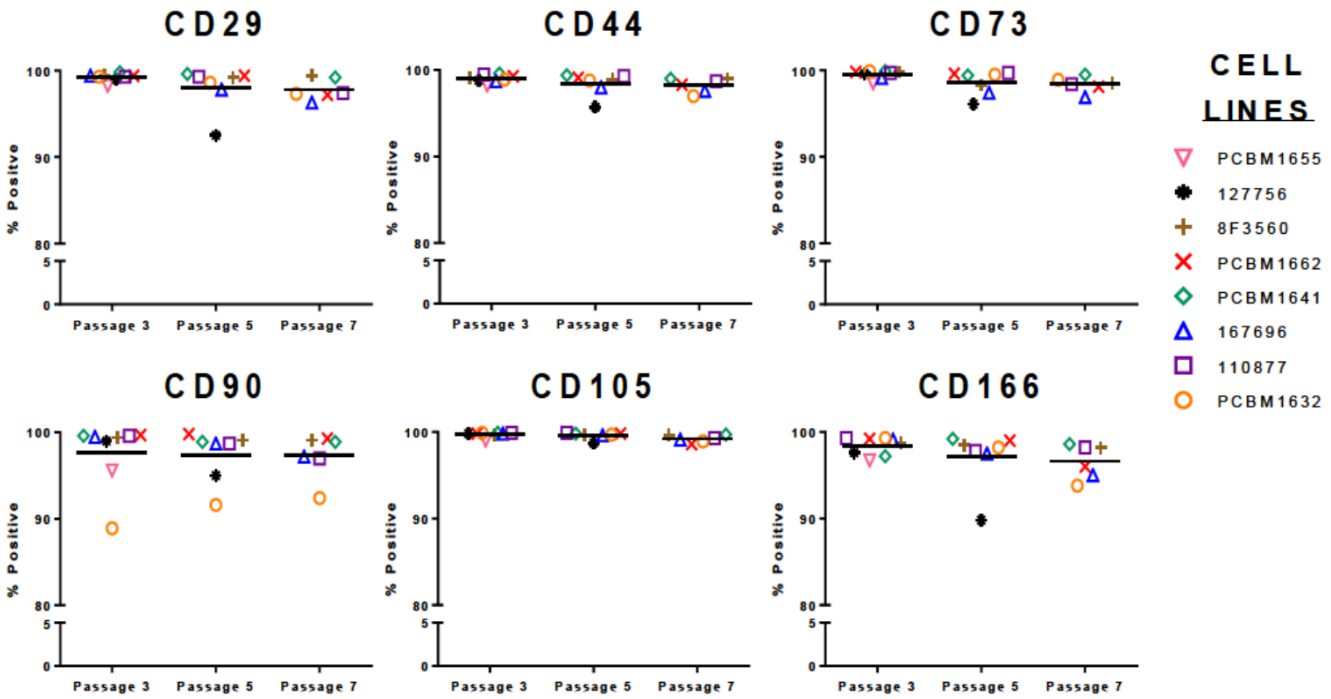
Source: Klinker et al. PNAS 2017

The heterogeneity of MSC's between donors could play a role in explaining the variability in efficacy observed between clinical trials of MSC's.

Moreover, effectively managing this inter-donor variability has proven difficult, as the activity of cell-based products, such as MSCs, can be multimodal and difficult to characterise. This makes it challenging to design product quality attributes and potency assays to manage it.

For instance, the diagram below (Figure 22) illustrates how key MSC surface markers showed minimal variation between different MSC lines and in-culture expansion passages, clearly in contrast to their biological heterogeneity.

Figure 22: Expression of Key MSC Surface Markers Across Different Cell Lines and Passages



Source: 2020 Remestemcel-L AM FDA Oncologic Drugs Advisory Committee (ODAC) Session

This exact concern was raised by the US Food and Drug Administration (FDA) in a 2020 Oncologic Drugs Advisory Committee (ODAC) meeting for the biologics licence application of Remestemcel-L, an allogeneic bone-marrow derived culture-expanded MSC therapy (Mesoblast, ASX: MSB)

Expansion Limitations / Potency

Manufacturing of conventional MSC therapies relies on in-culture cell expansion, which is when donor MSC's are replicated. This is required due to small number of cells extracted from each donor (~20,000 cells yielded), and the large number of cells required for each course of treatment (up to ~1 billion cells). Moreover, treatments can require multiple courses of MSCs.

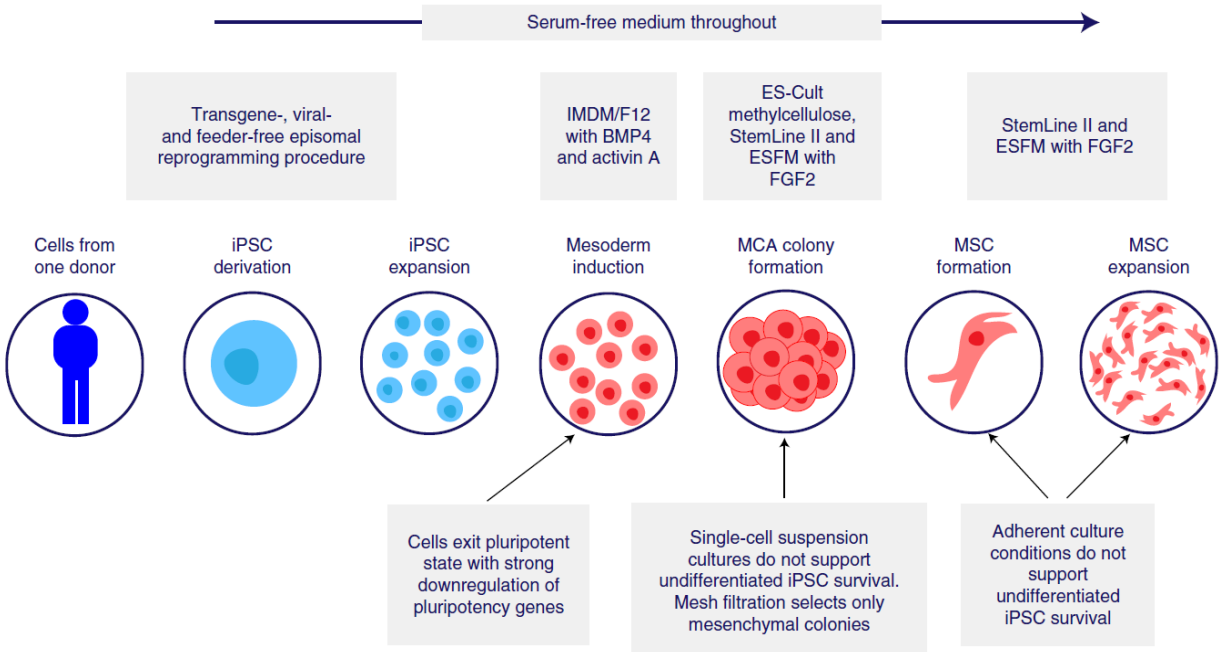
This presents a key issue, as there is a limitation to how much MSC's can be expanded. Moreover, studies have shown the potency of MSC's, defined by select characteristics, decreases with expansion. This is illustrated in Figure 21, which shows the immunosuppressive capacity of MSC's declines with in-culture duration.

This could similarly explain the variable results seen among clinical trials of MSC's. For instance, small investigator led trials are likely using a minimally expanded MSC therapy as they don't require many doses. However, commercial scale manufacturing may require significantly more expansion which could material alter the potency of the therapy.

Solution: Cymerus Technology

CYP has developed a unique patented manufacturing platform, Cymerus (Figure 23), which enables the production of a nearly unlimited amount of MSCs from a single donor – without losing potency or facing issues with consistency.

Figure 23: Cymerus Manufacturing Process



Source: Bloor AJC et al. 2020 ; IMDM: Iscove's modified Dulbecco's medium; F12: Ham's F12 nutrient mixture; BMP4: bone morphogenic protein-4; ESFM: endothelial serum-free medium.

The Cymerus platform brings together several breakthroughs in cellular biology, namely induced Pluripotent Stem Cells (iPSCs) and a recently identified MSC precursor, mesenchymoangioblasts (MCAs). Originally developed at the University of Wisconsin-Madison, a globally recognized leader in stem cell research, Cymerus has since been refined in-house by CYP.

MSCs produced by the Cymerus platform meet the International Society for Cell and Gene Therapy's criteria for multipotent MSCs. CYP has demonstrated that its manufacturing process is highly efficient, yielding a homogeneous population of MSCs characterized by the markers $CD105^{+}$, $CD73^{+}$, $CD90^{+}$, $CD43/45^{-}$, $CD31^{-}$, and $HLA\text{-}DR^{-}$. Moreover, global gene expression (transcriptome) analysis conducted by CYP on its MSCs has shown a high degree of consistency in gene expression and isoforms across different production batches. We believe this makes CYP's MSC product superior to conventional donor-derived products.

Induced Pluripotent Stem Cells (iPSCs)

The use of induced Pluripotent Stem Cells (iPSCs) enables Cymerus to overcome the challenges associated with conventional donor-derived MSC manufacturing, such as donor variability and limited cell supply.

iPSCs are stem cells generated from mature somatic cells. These cells are capable of transforming into any cell type within the human body while maintaining an almost infinite capacity for self-replication without changing. However, unlike its counterpart embryonic stem cells (ESCs), which are associated with significant ethical issues, iPSCs are derived from adult donor cells, and as a result avoid these issues. We separately note CYP's intellectual property position also covers the use of ESCs to generate MSCs.

The process of generating iPSCs was originally pioneered in 2006, a breakthrough that later earned a Nobel Prize. While first generation iPSC manufacturing methods were unsuitable for therapeutic use, newer methods have since been developed, enabling their application in therapy manufacturing technology like Cymerus. We note there are a number of other companies developing therapies using iPSCs, such as BlueRock Therapeutics (wholly-owned subsidiary of Bayer AG), Opsis Therapeutics (joint venture with FUJIFILM Cellular Dynamics), and Astellas Pharma (public, TYO: 4503). However, there are no other companies currently developing iPSC-derived MSCs, likely due to CYP's comprehensive intellectual property coverage.

The Cymerus platform utilises iPSCs, generated from a single donor's cells, to produce a near unlimited supply of MSC-precursor cells, mesenchymoangioblasts (MCAs). These MCA cells are subsequently used to generate MSCs, which are then expanded in-culture to generate the final MSC therapy product.

CYP has stated they can manufacture all of the MSCs that it will ever need from a single Master Cell Bank of iPSCs – derived from a single donor, in just one blood donation.

iPSCs used in the Cymerus platform are generated by reprogramming peripheral blood mononuclear cells, sourced from a single healthy donor. CYP's iPSC reprograming process utilises episomal, non-integrating, oriP/EBNA1-based plasmids.

CYP has validated the genetic stability of the iPSCs it uses in its Cymerus platform. Namely, as part of its Phase 1 study of CYP-001, the company demonstrated there were no differences in its iPSCs before and after 10-passages of in-culture expansion, as verified by comparative genomic hybridization (CGH) and single-nucleotide polymorphism (SNP) analysis. Moreover, CYP demonstrated its iPSCs showed no mutations of known or potential clinical significance, using a comparison to a reference genome.

Furthermore, as a precaution to mitigate any concerns around the risk of teratoma formation or aberrant differentiation in vivo of CYP's MSCs, the company specifically designed the Cymerus platform to incorporate various protocols which ensure the final MSC product is absent of any residual iPSCs.

Mesenchymoangioblast (MCA)

Mesenchymoangioblasts (MCAs) are a class of early clonal mesoendodermal precursor cells, which makes them a common precursor for both MSCs and endothelial cells. Importantly, the use of MCAs enables the production of well-defined MSCs that express markers of the lateral plate mesoderm but not those of the paraxial or intermediate mesoderm.

MCAs were first identified by Professor Igor Slukvin, one of the founders of CYP, and his team at University of Wisconsin-Madison. The process of generating MSCs from MCAs was subsequently patented and is now owned by CYP. Importantly, given MCAs are an MSC precursor cell, no one can use iPSCs (or ESCs) to generate MSCs without infringing on CYP's intellectual property.

Commercialisation

CYP has outlined a commercialisation strategy centred around partnering/licensing.

The company believes there is potential for multiple partnerships, covering its several products in development. Moreover, CYP has stated the Cymerus platform is available to partners pursuing other indications, and or, engineered MSC applications.

CYP has Attracted Significant Commercial Interest in the Past

In 2017, the company entered into a strategic development and commercialisation agreement with Fujifilm corporation for its lead asset, CYP-001, in acute GvHD. As part of this agreement, Fujifilm was granted an option for the right to exercise an exclusive, worldwide license to market and sell CYP-001 in acute GvHD. If exercised, CYP would be eligible to receive up to $60m in milestone payments and double digit royalties on net sales. Fujifilm additionally took at ~$4m strategic equity stake in the company, which it still holds to this day.

Notably, this agreement was done on preclinical data alone, prior to the commencement of the phase 1 acute GvHD trial. Likely also explaining the relatively small deal size.

In July 2019, CYP announced it had received an indicative, non-binding and conditional $2.00 per share cash takeover from major Japanese conglomerate, Sumitomo Group. Which implied a ~$217 million equity value.

However, in August 2019, Fujifilm exercised its option for a worldwide license of CYP-001 in acute GvHD. We believe this outcome likely contributed to Sumitomo withdrawing its $2.00 takeover offer a few weeks later, as CYP-001 in aGvHD was the company's most advanced asset.

Further complicating matters, in 2021 during the COVID-19 pandemic, Fujifilm opted to restructure the agreement into a manufacturing agreement and return the rights for CYP-001 in acute GvHD back to CYP. We speculate Fujifilm made this move as it appeared to have strategically refocused to manufacturing, rather than therapy development, as evident by its acquisition of Cellular Dynamics.

Industry Licensing Activity

There has been notable licensing activity in stem cell space in recent years (Figure 24).

As shown in the table, some of these licensing deals have featured upfront payments as high as US$50 million, with total deal values in excess of US$1 billion.

Moreover, there are a number of deals related to iPSCs in particular.

Potential Major Industry Catalysts Ahead

We anticipate that commercial activity in the MSC space could significantly increase if Mesoblast's (ASX: MSB) RYONCIL (Remestemcel-L) therapy receives FDA approval.

Mesoblast is expected to receive a decision from the FDA on its resubmitted BLA on or before January 7th 2025. Approval would grant RYONCIL marketing approval as a treatment for pediatric steroid-resistant acute GvHD. We believe there is a strong likelihood of approval, given the recent and unexpected reversal from the FDA indicating that Mesoblast had sufficient data to resubmit.

Importantly, we note that this approval would not compete with CYP, as it would apply only to pediatric steroid-resistant acute GvHD—a small subset estimated to number in the hundreds of patients. Furthermore, while the FDA may be open to approving RYONCIL for this ultra-rare condition due to the significant unmet need, we believe Mesoblast will still face challenges in pursuing approval for adult steroid-resistant acute GvHD and other larger indications.

Figure 24: Select Stem Cell Licensing Deals

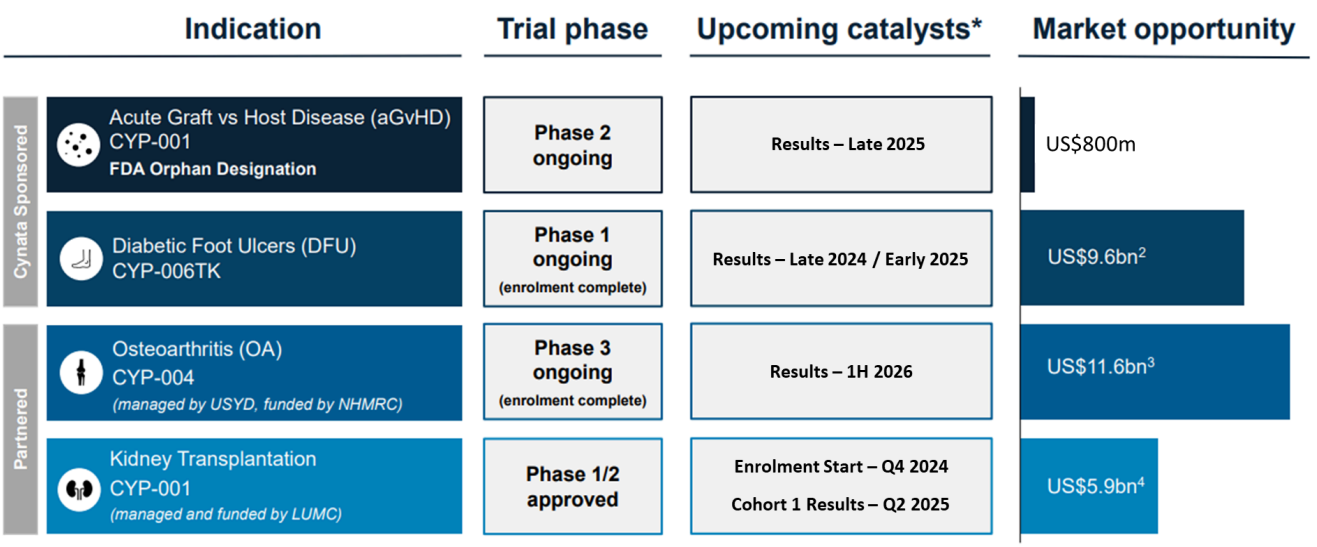
Year	Licensee	Licensor	Drug/Asset	Indication	Area	Stage	Upfront (US$M)	Milestone (US$M)	Total Deal (US$M)	Royalty Rate	Region
2016	Takeda	TiGenix	CX601	Fistulas; Crohn's	MSC	Ph 3	28	395	423	Double-digit	Ex-USA
2016	BMS	Evotec SE	Various	Various; Neurology	iPSC	n.d.	45	250	295	Double-digit	Worldwide
2016	BMS	Evotec SE	Various	Various; Neurology	iPSC	n/a	50	4,000	4,050	Tiered	Worldwide
2017	Cynata	Fujifilm	CYP-001	GvHD	MSC	Ph 1	3	43	46	10%	Worldwide
2017	TiGenix	Mesoblast	n.d.	Fistulae	MSC	n.d.	6	18	24	Single-digit	Worldwide
2019	Fate Therap.	Janssen	Various	Various; Oncology	iPSC	n.d.	50	3,000	3,050	Double-digit	Worldwide
2019	ReNeuron	Fosun Pharma	Various	Various	Stem cell	n.d.	8	97	105	12-14%	China
2019	Grünenthal	Mesoblast	MPC-06-ID	CLBP	MSC	Ph 3	15	985	1,000	Double-digit	EU/LatAm
2020	Novartis	Mesoblast	Remestemcel-L	ARDS	MSC	Ph 3	50	1,255	1,305	Double-digit	Worldwide
2020	Astellas Pharma	Adaptimmune Therap.	Various	Various	Stem cell	n.d.	50	848	898	single-digit	n/a
2020	Allogene Therap.	Notch Therap.	Various	Various	Stem cell	n.d.	10	294	304	n.d.	n/a
2024	Lucy Biotech	ENCell	EN001	Various	MSC	Ph 1b	2	18	20	n.d.	Select Asia*

*Source: Company announcements, media articles, EH analysis; *Hong Kong, Taiwan, Macau, Vietnam, Thailand, and Singapore*

Clinical Development

CYP currently has multiple clinical trials underway (Figure 25), with an initial lead focus in acute graft vs host disease (aGvHD), a rare disease with granted orphan drug designation.

Figure 25: CYP Clinical Development Pipeline



Source: company presentation, quarterly report, EH analysis

Although aGvHD is not the largest indication, it represents a readily accessible opportunity for CYP to validate its Cymerus platform. This will serve as an important initial step in paving the way for the pursuit of significantly larger indications.

The current clinical programs can be grouped into company sponsored trials and investigator led, the latter being clinical trials run and funded by external clinicians and researchers. While these may not be the commercial focus of CYP, these programs come at no cost to the company.

The same iPSC-MSC product is used across all clinical programs, with the main difference being the route of administration. In CYP-001, MSCs are administered through an infusion, CYP-006TK with a seeded dressing, and finally CYP-004 through intra-articular injections. Additionally, there are differences in the dosage of MSCs between programs.

We explore each of these clinical programs in this research.

Figure 26: Leading Research Partnerships

Source: company presentation

Graft vs Host Disease (GvHD): CYP-001

CYP's lead program, CYP-001, is being evaluated as a novel intravenous (IV) treatment for acute graft vs host disease, a rare disease with granted orphan drug designation.

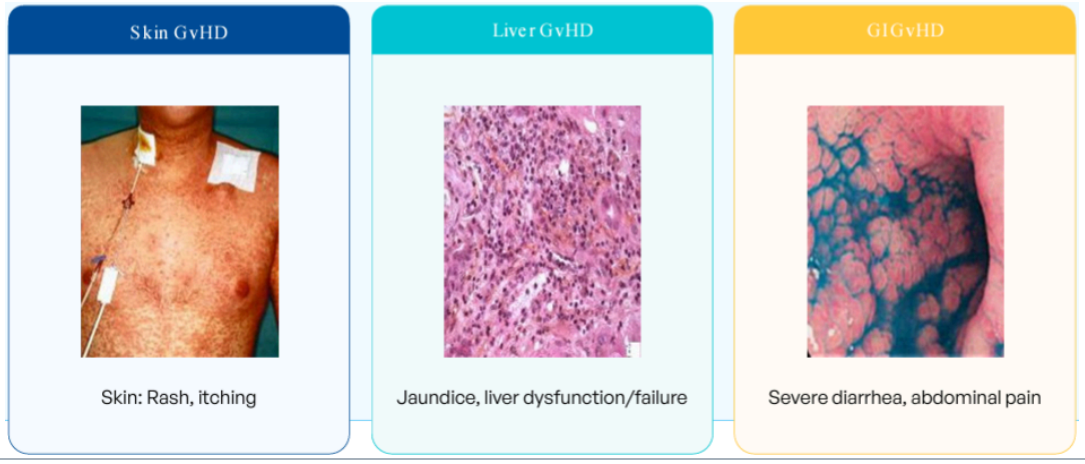
There remains a significant unmet need present, with limited effective and tolerable treatment options, and overall poor survivability.

Graft vs Host Disease Overview

Graft vs Host Disease (GvHD) is a potentially life-threatening complication of an allogeneic hematopoietic stem cell transplantation (HSCT), also known as a bone marrow transplant. Although lesser known, GvHD can also occur following a transfusion of non-irradiated blood or transplantation of lymphoid cell rich organ (e.g. liver).

The GvHD occurs when the transplant donor stem cells (the "graft"), attack healthy cells in the body (the "host"), leading to symptoms ranging from mild to moderate to severe, and potentially fatal, which affect the skin, GI tract, liver, and other organs (Figure 27).

Figure 27: Graft Versus Host Disease Presentation



Source: MaaT Pharma Investor Presentation

In addition to the significant associated disability and reduction in quality of life, acute GvHD is associated with high rates of mortality, such that:

- Grade II acute GvHD has a ~70% 1-year overall survival rate; and
- Grade III-IV acute GvHD has ~40% 1-year overall survival rate (ie. 60% mortality)

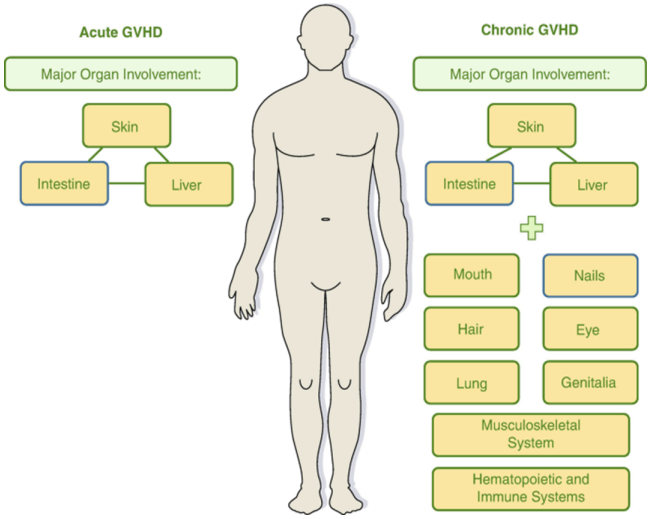
Moreover, in patients who develop steroid resistant acute GvHD, mortality rates can reach as high as 90%. In addition to being associated with significant extended hospital stays.

Factors which can affect the prevalence and severity of GvHD, include but are not limited to the donor-host matching (e.g. unmatched donors, human leukocyte antigen (HLA) disparity, and sex mismatching), HCT source type and handling, and the conditioning regimen used (e.g. chemotherapy used as part of HCT procedure).

GvHD can be subclassified as either being acute or chronic. These classifications were originally defined by the timing of the GvHD onset, with acute being GvHD symptoms within 100 days of an allogeneic HCT procedure, and the latter being when symptoms present more than 100 days after.

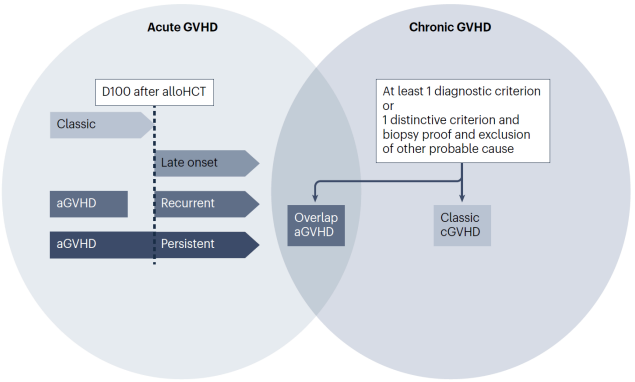
However, this classification has since changed and is now based on the features of the disease, including which organs are involved. For instance, acute GvHD typically affects the skin, liver and gastrointestinal (GI) tract, whereas chronic GvHD can affect any organ in the body and has no time limit on when it is diagnosed (Figure 28).

Figure 28: Acute vs Chronic GvHD, Organ Involvement



Source: Ahmed, Z., Vierling, J.M. (2020)

Figure 29: GvHD Subclassification classification diagram



Source: Malard, F., Holler, E., Sandmaier, B.M. (2023)

The current subclassification of GvHD is defined as follows (Figure 29):

- **Acute classic GVHD** – Symptoms presenting within 100 days of an allogeneic HCT, with typical clinical features of acute GVHD;
- **Persistent, recurrent, or late-onset acute GVHD** – defined by the clinical features of classic acute GVHD but with symptoms presenting 100 days of an allogeneic HCT;
- **Classic chronic GVHD** – symptoms presenting 100 days after an allogeneic HCT, with the classic clinical features of chronic GVHD; and
- **Overlap syndrome** – This can occur at any time after an allogeneic HCT procedure and can have features of both acute and chronic GVHD.

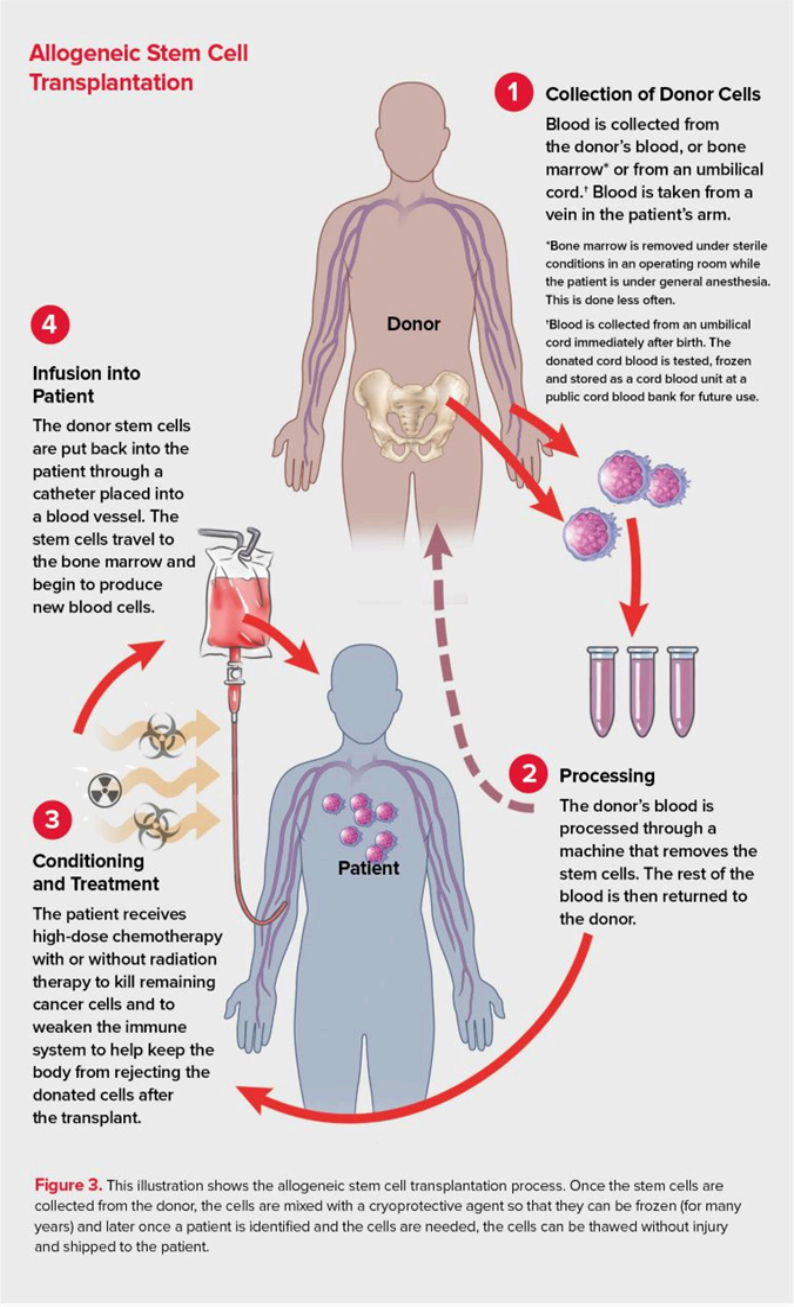
In the context of CYP, we are focused on acute GvHD.

Allogeneic Hematopoietic Stem Cell Transplantation (HCT)

Allogeneic (donor sourced) hematopoietic stem cell transplantation (HCT), sometimes called an Allogeneic bone marrow transplant, is a potentially curative procedure for certain life-threatening malignant and non-malignant blood or bone marrow disorders, such as leukemia, myelodysplastic syndromes and myeloproliferative neoplasms.

An allogeneic HCT procedure broadly involves administering a patient with healthy stem cells from a donor, which can be either related or unrelated, to augment the production of healthy blood cells, and in certain cases also enable the destruction of tumour cells.

Figure 30: Allogeneic Hematopoietic Stem Cell Transplantation Overview



Source: Leukemia & Lymphoma Society

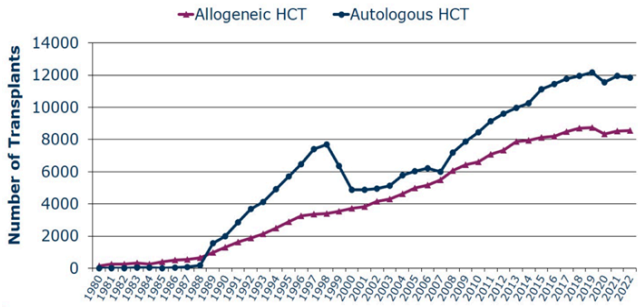
Prior to being administered donor hematopoietic stem cells, the patient will first receive a conditioning treatment which can consist of either chemotherapy, total body irradiation, or a combination of both. This treatment eliminates the damaged or cancerous cells, to allow the new cells to replace the patient's bone marrow and begin producing new blood cells.

This conditioning treatment also has the effect of weakening the patient's own immune system, which helps facilitate the receival of donor stem cells, and reduce the likelihood, and or, severity of graft vs host disease. However, as we explore, the conditioning procedure itself is a driver of GvHD.

While allogeneic HCT presents a potentially curative procedure for numerous patients, its broad use remains limited by the potentially severe and, in certain cases, lethal treatment-associated side effects, with graft vs host disease being a major contributor.

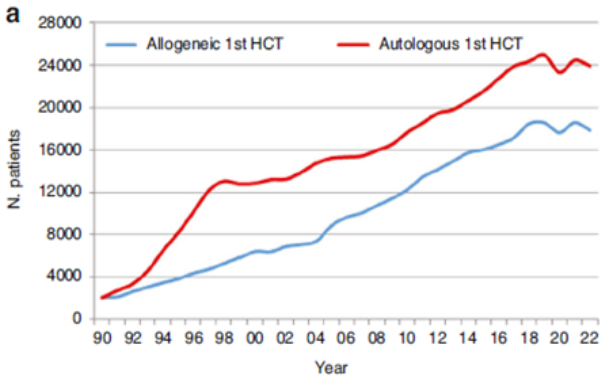
There are roughly ~8,500 allogeneic HCT performed in the United States annually as of 2022 (Figure 31), according to the Center for International Blood and Marrow Transplant Research (CIBMTR).

Figure 31: US Allogeneic HCT Procedures per annum



Source: Center for International Blood and Marrow Transplant Research (CIBMTR)

Figure 32: EU Allogeneic HCT Procedures per annum



Source: European Society for Blood and Marrow Transplantation (EBMT)

This figure is significantly higher in Europe, with ~19,000 allogeneic HCT procedures performed annually as of 2022 (Figure 32), according to a survey across 689 centres by the European Society for Blood and Marrow Transplantation (EBMT).

The majority of allogeneic HCT Procedures occur in the United States and Europe due to the accessibility and costs associated with these complex procedures.

Acute GvHD Diagnosis

Acute GvHD is diagnosed and graded by its severity based on a clinical assessment of symptoms alongside laboratory tests and biopsies (Figure 21 and 34)

Figure 33: Clinical Presentation Across Key Organs

Organ	Clinical presentation	Characteristics
Skin	• maculopapular skin rash	• usually the first organ involved and the most commonly affected organ • characterised as a diffuse, maculopapular rash with predilection for the palms and soles, ears, neck and dorsal surfaces of the extremities and malar regions
Liver	• jaundice	• staged based solely on the serum bilirubin level • liver disease caused by GVHD may be difficult to distinguish from other causes of liver dysfunction such as veno-occlusive disease, drug toxicity, viral infection, sepsis, cholestasis secondary to total parental nutrition therapy or iron overload
Upper gastrointestinal tract	• nausea and vomiting • anorexia	• a positive upper gastrointestinal biopsy in this clinical setting is confirmatory (stage 1)
Lower gastrointestinal tract	• watery or bloody diarrhoea • severe crampy abdominal pain	• characteristically presents as secretory diarrhoea that can progress to grossly bloody stools with severe abdominal pain and/or ileus in its most severe form (stage 4)

Source: eviQ website

Figure 34: Overall GvHD Grading and Individual Organ Grading System

	Skin	Liver	Upper GI	Lower GI
Stage				
0	no active (erythematous) GVHD rash	bilirubin < 34 micromol/L	No or intermittent nausea, vomiting or anorexia	diarrhoea < 500mL/day or < 3 episodes/day
1	maculopapular rash < 25% of BSA	bilirubin 34 - 50 micromol/L	Persistent nausea, vomiting or anorexia	diarrhoea 500 - 999mL/day or 3 -4 episodes/day
2	maculopapular rash 25 - 50% of BSA	bilirubin 51 - 102 micromol/L		diarrhoea 1000 - 1500mL/day or 5 - 7 episodes/day
3	maculopapular rash > 50% of BSA	bilirubin 103 - 255 micromol/L		diarrhoea > 1500mL/day or > 7 episodes/day
4	generalised erythroderma (> 50% BSA) plus bullous formation and desquamation > 5% of BSA	bilirubin > 255 micromol/L		severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)

Grade	Skin		Liver		Lower GI		Upper GI
0	No stage 1 - 4 of any organ						
I	stage 1 - 2		none		none		none
II	stage 3	and/or	stage 1	and/or	stage 1	and/or	stage 1
III	stage 0 - 3	with	stage 2 - 3	and/or	stage 2 - 3	and/or	stage 0 - 1
IV	stage 4	or	stage 4	or	stage 4	with	stage 0 - 1

Source: eviQ website

Acute GvHD Incidence

Acute GvHD occurs in between 30% to 50% of allogeneic HCT procedures, with some figures suggesting it is as high as 80%.

In a study by the Blood and Marrow Transplant Clinical Trials Network, the cumulative 100-day incidence of acute GvHD was 62% as reported by the centres, and 45% after validation by a committee.

Moreover, it is estimated ~50% of patients will develop steroid resistant (SR) acute GvHD.

Figure 35: Estimated Acute GvHD Prevalence

	Units	Europe	United States	Combined
Allogeneic HCT Procedures	#	19,000	8,500	27,500
(x) Est Acute GvHD	%	50%	50%	
Acute GvHD	**#**	**9500**	**4250**	**13,750**
(x) Est Steroid Resistant	%	50%	50%	
SR-Acute GvHD	**#**	**4,750**	**2,125**	**6,875**

Source: EH estimates, CIBMTR, EBMT

We estimate there circa 13,750 annual cases of acute GvHD across the United States and Europe alone, based on the annual number of allogeneic HCT procedures and prevalence rates of acute GvHD (Figure 35).

Furthermore, we estimate ~6,900 annual cases of steroid resistant acute GvHD across both regions.

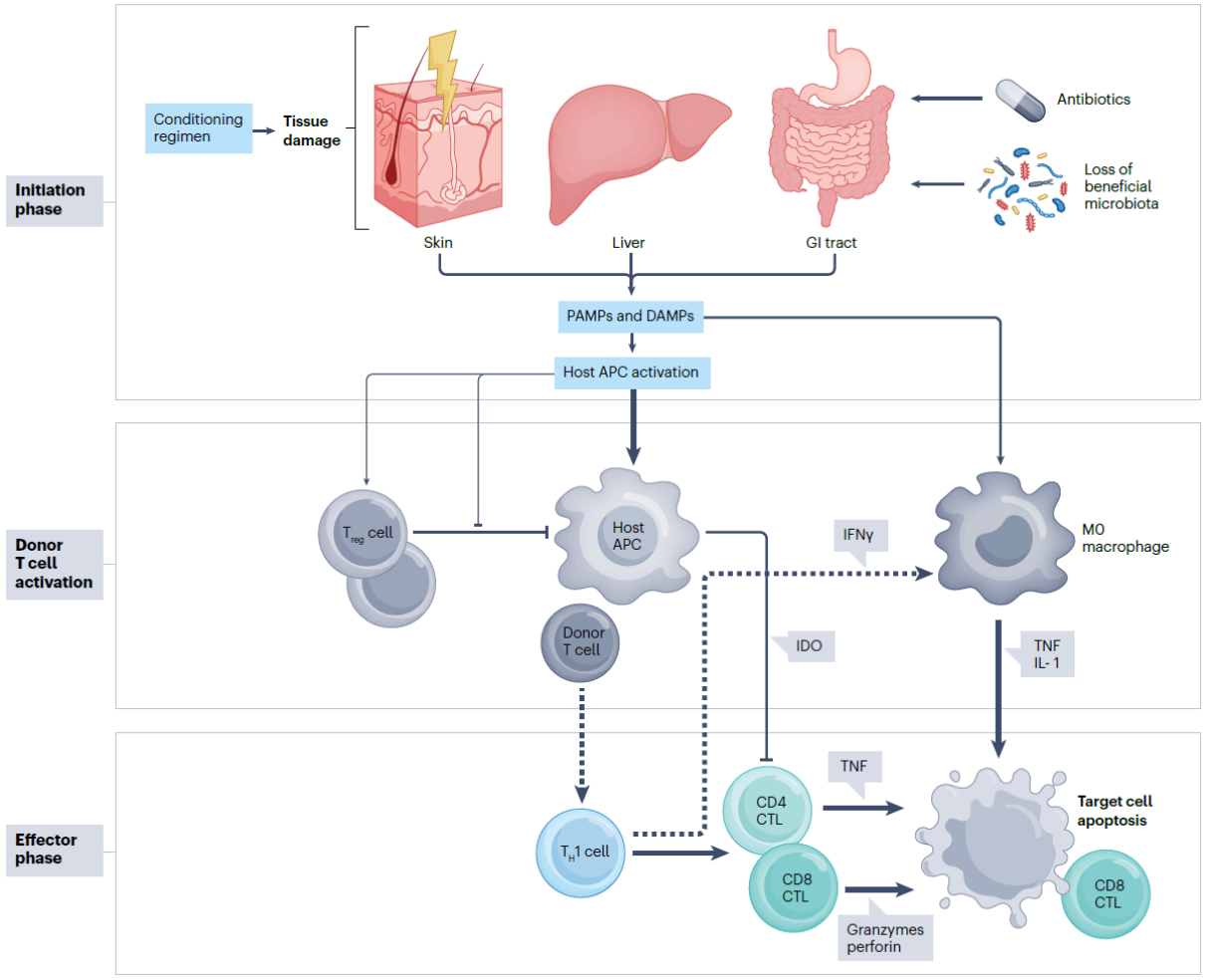
Acute GvHD Pathophysiology

The pathophysiology of acute GvHD is a complex interplay between the pre-transplantation conditioning regimen and the immune reaction to transplanted donor cells.

This process can be broken down into three stages (Figure 36):

1. **Initiation Phase** – During the conditioning phase, prior to receiving donor hematopoietic stem cells, patients first receive chemotherapy and/or total body irradiation, which damages host tissue. This damage releases pro-inflammatory stimuli such as damage-associated molecular patterns (DAMPs) which themselves lead to the release of cytokines such as necrosis factor (TNF) and type I interferon (IFNγ), and pathogen-associated molecular patterns (PAMPs) like lipopolysaccharide. These then activate host antigen-presenting cells (APC). Moreover, antibiotic use during the conditioning phase potentially impacts immune homeostasis.
2. **Donor T Cell Activation** – Activated host APC's then go onto activate effector cells, including alloreactive donor CD4+ and CD8+ T cells.
3. **Effector Stage / End Damage** – In the final stage, these activated effector T cells, mediated by pro-inflammatory cytokines, kill target tissue via apoptosis. Further, this immune response can result in inflammatory-associated cell death, like necroptosis, which perpetuates a cycle of cell death and inflammation. All of which contributes acute GvHD.

Figure 36: Acute GvHD Pathophysiology Overview



Source: Malard, F., Holler, E., Sandmaier, B.M. (2023)

Acute GvHD Standard of Care: Limited & Ineffective

Acute GvHD patients are in desperate need of new treatment options, as evident by the prevalent high rates of morbidity and mortality.

The current standard of care relies on high-dose steroids and other immunosuppressive drugs as a first line therapy (Figure 37). Only half of patients demonstrate an initial response to steroids, with even fewer (~30%) showing a durable enough response to subsequently withdraw from them.

Moreover, high-dose steroids and other immunosuppressive drugs are associated with severe and potentially lethal side effects. These include increased risk of infectious complications, as well as non-infectious side effects such as diabetes, osteoporosis, aseptic osteonecrosis, amyotrophy and other symptoms of iatrogenic cushing syndrome.

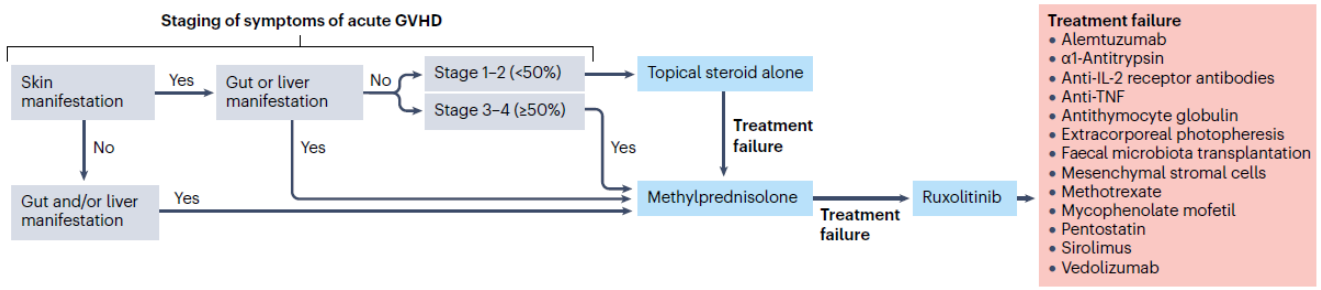
Acute GvHD that is treated with steroids and continues to progress by day three or fails to see any disease improvement by day seven, is considered to be steroid-refractory or steroid resistant.

There is currently only one FDA and EMA approved treatment for steroid-resistant or dependant acute GvHD, Ruxolitinib, a Janus kinase 1 and 2 (JAK1 & JAK2) inhibitor.

Ruxolitinib secured FDA approval in 2019. In a phase 3 study, Ruxolitinib demonstrated a 62% overall response by day 28 compared to the best available treatment response of 39% ($p<0.001$). However, the durable response of Ruxolitinib quickly dropped off to ~39% by day 56, which otherwise implies almost two-thirds of patients required a third line therapy, or died. Moreover, Ruxolitinib has a very poor safety profile with significant and serious side effects.

Clearly, there is an unmet need for improved acute GvHD treatments, and in particular, treatments for steroid resistant acute GvHD.

Figure 37: Acute GvHD Treatment Algorithm

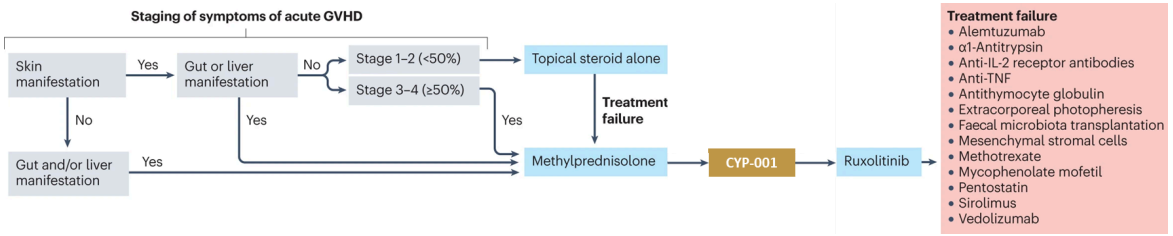


Source: Malard, F., Holler, E., Sandmaier, B.M. (2023)

CYP-001: Potential Second Line (2L) Acute GvHD Treatment

CYP's novel intravenous (IV) iPSC-derived MSC therapy, CYP-001, shows promise as a potential second-line (2L) therapy for patients with high-risk acute GvHD alongside steroids, which we anticipate will be the first approved indications. This label would also make CYP-001 a first-line (1L) therapy for patients with steroid-resistant acute GvHD

Figure 38: Anticipated Acute GvHD Treatment Algorithm, Subject to Approval



Source: Malard, F., Holler, E., Sandmaier, B.M. (2023); EH analysis

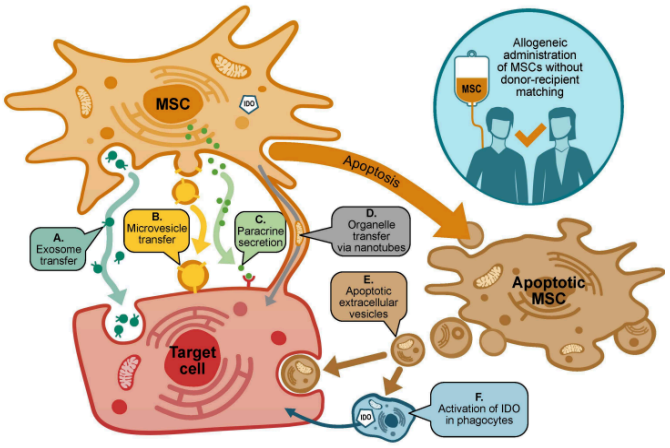
Clinician feedback indicated if a new therapy could match the efficacy of Ruxolitinib, with fewer side effects, then it would offer a significant advancement. Preliminary data on CYP-001 suggests it could meet this criterion, supporting this proposed treatment positioning.

The multifaceted immunomodulatory mechanism of action, in combination with its excellent established safety profile makes MSC's well suited for treating GvHD.

MSC are thought to work in GvHD by promoting an immunosuppressive and immunoregulatory environment. They may potentially influence host immune cells, including T cells, B cells, natural killer cells, monocytes, and dendritic cells, as well as host tissues susceptible to GvHD damage, such as the skin, gastrointestinal tract, and liver. This influence is mediated through the secretion of cytokines, chemokines, growth factors, and extracellular vesicles.

Notably, MSC's continuously secrete indoleamine 2,3-dioxygenase (IDO), which suppresses the proliferation of allogeneic T cells. Moreover, the secretion of IDO is upregulated when MSC's are activated in the presence of inflammatory cytokines, such as interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α). This feedback loop enables MSC's to regulate the immune response, rather than just bluntly suppressing it – which could have adverse effects.

Figure 39: MSC Mechanism of Action in GvHD



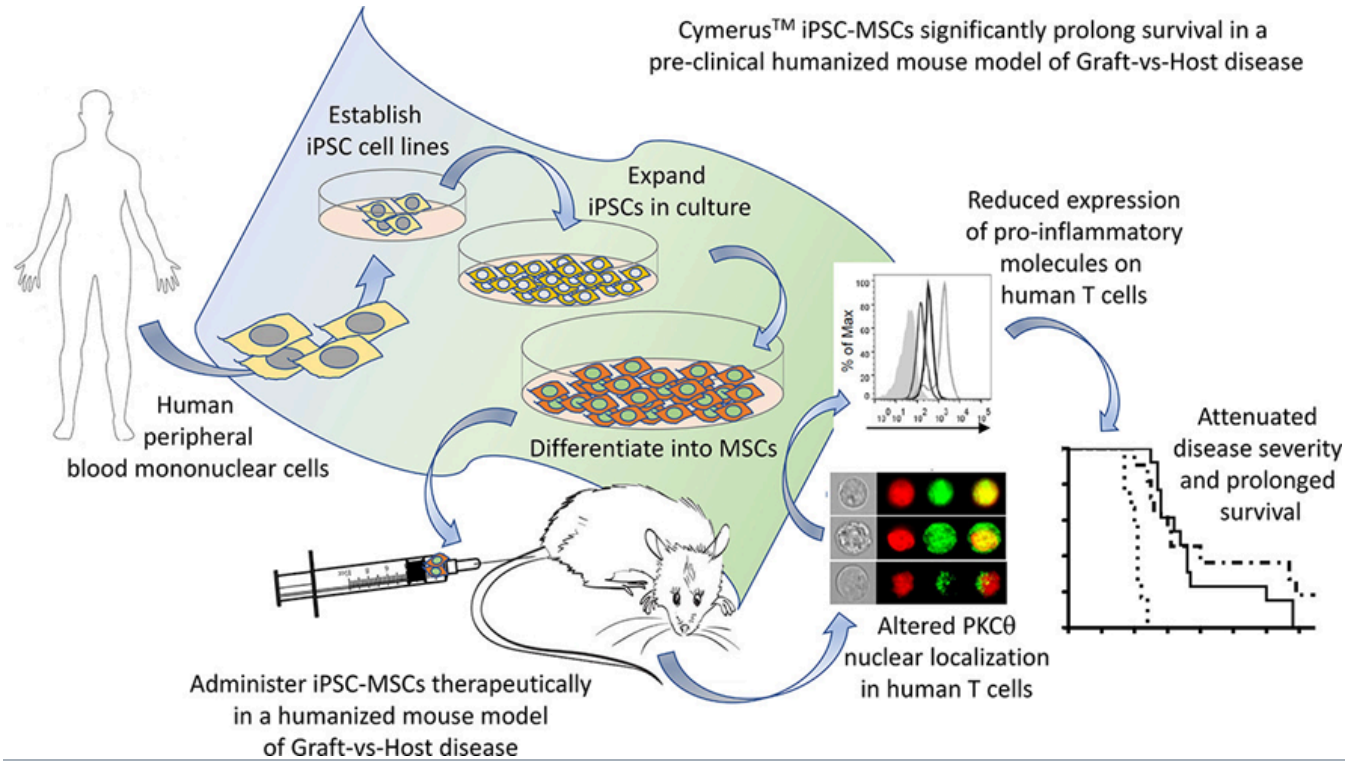
Source: Kelly and Rasko (2021)

We note the excellent safety profile of MSC's could enable a therapy like CYP-001 to potentially elevate into a first line (1L) treatment for higher risks acute GvHD patients, in the longer term. Furthermore, supplying this therapy would be feasible with CYP's highly-scalable manufacturing platform, Cymerus.

Preclinical Development

In preclinical studies, CYP demonstrated that administration of CYP-001 altered the nuclear localization of Protein Kinase C theta (PKCθ) in human T cells (which can affect immune response), reduced the expression of pro-inflammatory molecules on human T cells, attenuated disease severity, and prolonged survival in a humanized mouse model of GvHD (Figure 40).

Figure 40: Preclinical Work Summary Diagram



Source: Ozay EI, Vijayaraghavan J, Gonzalez-Perez G, Shanthalingam S, Sherman HL, Garrigan DT Jr, Chandiran K, Torres JA, Osborne BA, Tew GN, Slukvin II, Macdonald RA, Kelly K, Minter LM (2019)

Phase 1 Clinical Study – Complete

CYP successfully completed a phase 1 clinical trial of CYP-001 in adults with steroid-resistant acute GvHD in 2018 (ID: NCT02923375). This was the first ever human clinical trial of iPSC-derived cells.

The multicentre, open-label, dose-escalation study evaluated the safety, tolerability and efficacy of two infusions of CYP-001 in 15 adults with steroid-resistant acute GvHD.

As typical for a phase 1 first in human trial, the primary endpoint was safety and tolerability.

The secondary objective of the study was to evaluate the efficacy of CYP-001. This was assessed based on the overall response (OR) rates to CYP-001 at days 28 and 100, as well as the overall survival (OS) rates of patients at days 28 and 100. We note day 28 is a standard used time point in acute GvHD clinical trials.

Furthermore, patients who completed the 100-day primary evaluated period subsequently entered into a 2-year safety and survival study. This study has since been completed.

In total, 16 subjects were screened and enrolled into the phase 1 study between 2017 and 2018. To be eligible, patients had to have Grade II-IV acute GvHD, and have steroid resistant acute GvHD based on the following criteria:

- The GvHD failed to respond/improve after at least 3 days' intravenous or oral treatment with an appropriate corticosteroid at a dose of at least 1 mg kg^{-1} d^{-1};
- The patient was treated with a steroid regimen and duration that is consistent with normal practice at the relevant clinical site; and
- The patient was considered to be steroid resistant in the opinion of the investigator.

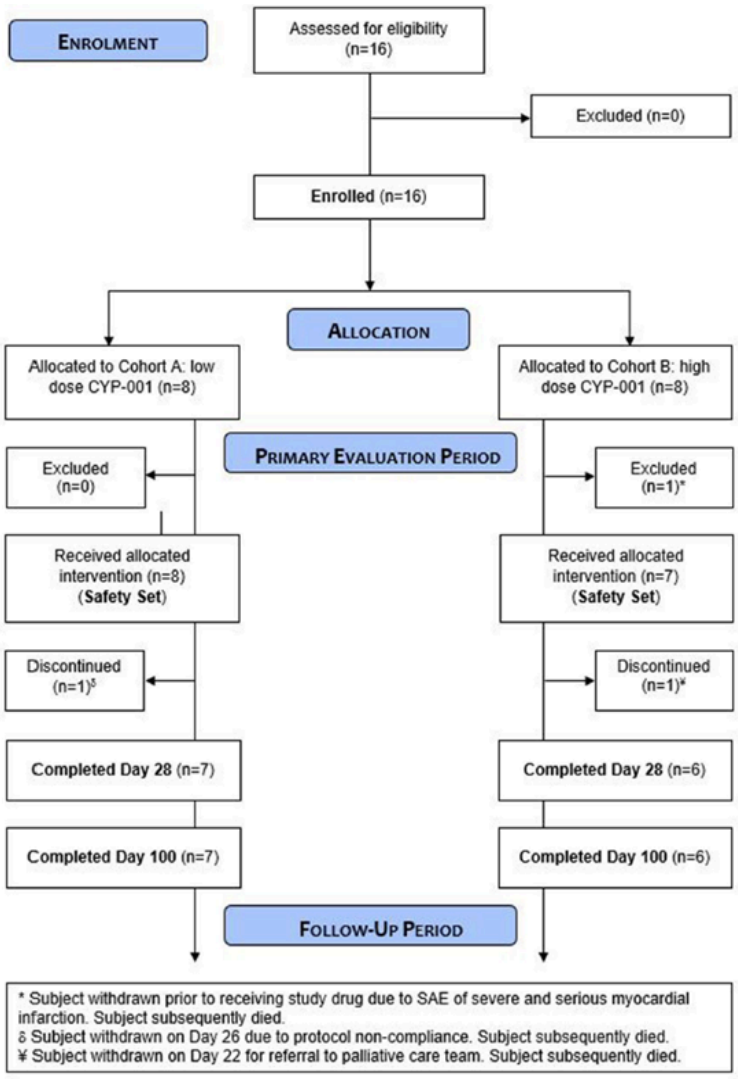
Throughout the study, patients received standard of care according to local site procedures.

Enrolled patients were subsequently assigned into two cohorts, cohorts A or B, which related to the dose of CYP-001 received. Such that:

- Cohort A Patients (n=8) received two doses of CYP-001, on days 0 and 7, up to a maximum $1x10^8$ cells; and
- Cohort B patients B (n=8) received the same CYP-001 dosing, up to a maximum $2x10^8$ cells.

We note one patient withdrew prior to receiving CYP-001 due to experiencing an unrelated a myocardial infarction, and was therefore excluded from analysis.

Figure 41: Phase 1 Clinical Trial Design Summary



Source: Bloor AJC et al. (2020)

Efficacy

Patients treated with CYP-001 demonstrated a strong and durable treatment response, which improved over time and compared favourably to both the current standard of care for steroid resistant acute GvHD, Ruxolitinib, and competitor therapies using traditional bone-marrow derived MSCs.

Figure 42: Key Phase 1 Results

Outcome measure	Cohort A, *n* (%)	Cohort B, *n* (%)	Total, *n* (%)
Best response by day 28			
CR	1 (12.5)	4 (57.1)	5 (33.3)
PR	4 (50.0)	2 (28.6)	6 (40.0)
OR	5 (62.5)	6 (85.7)	11 (73.3)
Best response by day 100			
CR	4 (50.0)	4 (57.1)	8 (53.3)
PR	3 (37.5)	2 (28.6)	5 (33.3)
OR	7 (87.5)	6 (85.7)	13 (86.7)
Time to first response (d)			
Median (range[a])	14 (3-60)	3 (3-38)	7 (3-60)
Time to best response[a] (d)			
Median (range[a])	60 (14-60)	14 (3-28)	21 (3-60)
OS at day 100	7 (87.5)	6 (85.7)	13 (86.7)

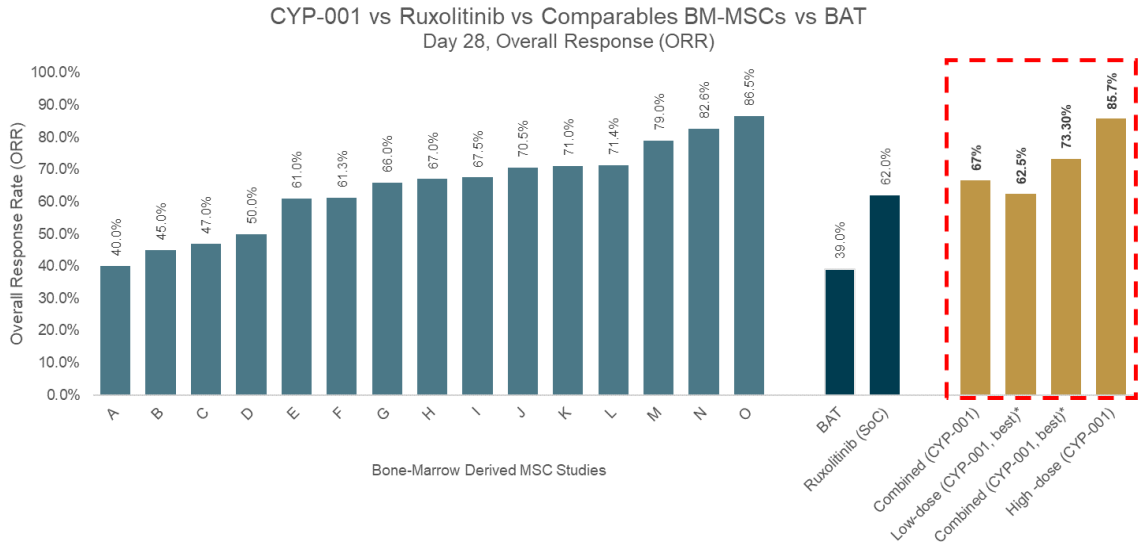
n, number of patients; first response, improvement by at least one aGvHD grade; best response, maximal improvement in aGvHD grade. [a]Upper end of range calculated only for those patients who responded within 100 days.

Source: Bloor AJC et al. (2020)

A total of 13 (~87%) of the total 15 enrolled survived through day 100. There were two patients who died, including one in cohort A on day 28 due to pneumonia, which was determined unrelated to CYP-001. A second patient, in cohort B, showed no improvement in acute GvHD and withdrew on day 22 to begin palliative care, and subsequently died.

The best overall response rate (ORR) for CYP-001 at day 28, was 62.5% in the low dose cohort (cohort A) and an impressive 85.7% in the high dose cohort (cohort B), with a combined 73.3% response (~67% combined overall response). This level of response compares very favourably to the day-28 overall response of Ruxolitinib, the best available therapy (BAT), and other studies using traditional bone marrow-derived MSCs (Fig 43).

Figure 43: Day 28 OR*: CYP-001 vs Ruxolitinib vs Comparable BM-MSCs vs Best Available Therapy (BAT)

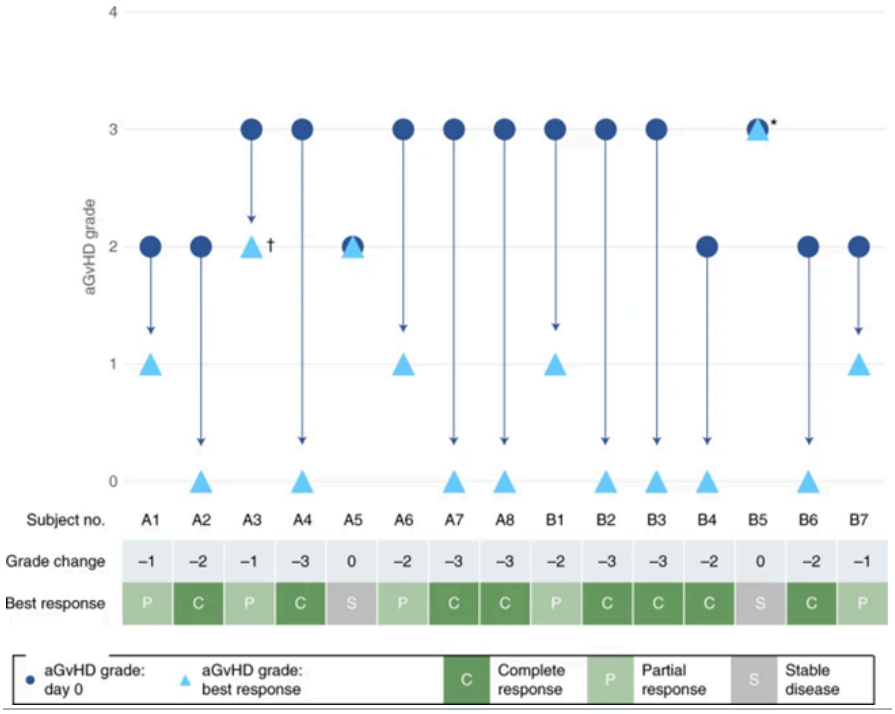


*Source: Bloor AJC et al. (2020), Elgaz S, Kuçi Z, Kuçi S, Bönig H, Bader P (2019), EH analysis, *Best ORR, BAT= best avail. therapy*

No patients in the trial experienced relapse after responding to CYP-001. However, one patient in the low-dose cohort, included in the best overall response assessment, achieved a partial response on days 12 and 21 but died from pneumonia on day 28.

Notably, subjects treated with CYP-001 only received two infusions each, compared to between 3 and 12 infusions each in the other bone-marrow derived MSC studies.

Figure 44: Day 100 Acute GvHD Status and Best Response Rates: CYP-001



Source: Bloor AJC et al. (2020)

By day 100, the best overall response improved to 87.5% in the low-dose cohort and remained stable at 85.7% in the high-dose cohort. Across both cohorts, 13 out of the 15 enrolled patients (~87%) reported a response. Of the two non-responders, one was the patient who withdrew on day 22 to enter palliative care. Excluding this patient would raise the best overall response rate to +90%.

CYP-001 demonstrated significantly better results compared to other bone marrow-derived MSC studies, which reported day 100 overall response rates ranging from 34.4% to 57.3%.

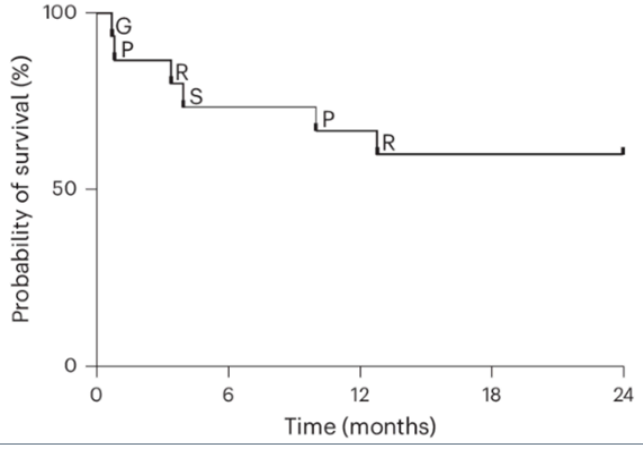
Furthermore, while Ruxolitinib, the current standard of care, did not report a day 100 overall response rate in its pivotal study, it did report a low 40% overall response rate at day 56. In contrast, CYP-001 showed a significantly higher ~73% best overall response rate (~67% overall response rate) at day 60 (the closest available time point).

Although this was a relatively small study, the data highlights a striking trend – CYP-001's response rate improves over time, in contrast to Ruxolitinib and the best available therapy which appears to diminish in effectiveness over longer time.

Additionally, by day 100, all patients treated with CYP-001 had either completely discontinued systemic steroids (n=7, ~47%) or were receiving a reduced dose (n=8, ~53%). Moreover, two patients who initially started the study on intravenous steroids had transitioned to oral steroids by day 100. This further highlights the tangible therapeutic benefits of CYP-001, as all patients began the study on a universal systemic corticosteroid regimen, alongside their concomitant acute GvHD standard of care medications.

Long term survival rates in patients treated with CYP-001 were equally impressive, with 9 of the 15 (~60%) enrolled patients surviving as of the 2-year follow up.

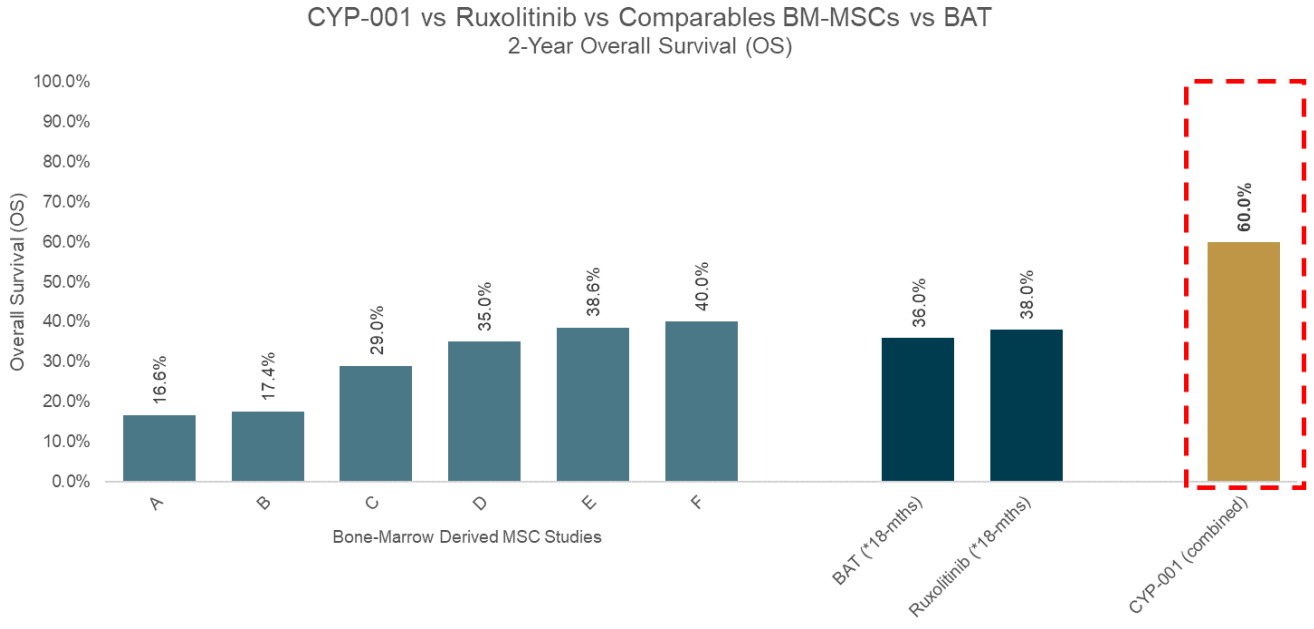
Figure 45: 2-year Combined Survival Rate: CYP-001



Source: Kelly K et al. (2024)

Despite the small sample size, CYP-001 resulted in significantly higher 2-year survival when compared to other bone-marrow derived MSC studies which reported 2-year overall survival rates ranging from 17% to 40%. Moreover, the standard of care, Ruxolitinib, reported only 38% survival at an earlier 18-month time point (its latest available data point), whereas CYP-001 showed 60% at the same time point (Figure 46).

Figure 46: 2-year OS: CYP-001 vs Ruxolitinib vs Comparable BM-MSCs vs Best Available Therapy (BAT)



Source: EH analysis, Kelly K et al. (2024), EH analysis, BAT= best available therapy

Safety and Tolerability

CYP-001 was safe and well tolerated, with no subjects discontinuing treatment due to adverse events.

Figure 47: Phase 1 Adverse Events Summary

Adverse event category	Cohort A, *n* (%)	Cohort B, *n* (%)	Total, *n* (%)
Treatment emergent AEs	8 (100.0)	7 (100.0)	15 (100.0)
Relationship to CYP-001 treatment[a]			
Definitely related	0 (0)	0 (0)	0 (0)
Probably related	0 (0)	0 (0)	0 (0)
Possibly related	2 (25.0)	2 (28.6)	4 (26.7)
Unlikely to be related	4 (50.0)	4 (57.1)	8 (53.3)
Not related	4 (50.0)	6 (85.7)	10 (66.6)
Intensity			
Mild	6 (75.0)	7 (100.0)	13 (86.7)
Moderate	6 (75.0)	5 (71.4)	11 (73.3)
Severe	4 (50.0)	1 (14.3)	5 (33.3)
SAEs	3 (37.5)	0 (0)	3 (20.0)
Adverse events leading to death	1 (12.5)	0 (0)	1 (6.7)

Source: Bloor AJC et al. (2020)

During the primary evaluation period, five adverse events—abdominal pain, diarrhea, febrile neutropenia, arthralgia, and renal impairment—were assessed as possibly related to CYP-001 dosing. These adverse events were considered to have a reasonable time relationship to the dosing, although we note they could also be attributed to the underlying disease or other medications.

Notably, no adverse events were assessed as probably or definitely related to CYP-001 dosing.

This safety profile was consistent in the 2 year follow up period, with no serious adverse events, tumours, or other safety concerns related to CYP-001 dosing reported.

Conversely, adverse reactions associated with the use of ruxolitinib, the standard of care, are common and severe. Serious/life-threatening (grade 3-4) adverse reactions are illustrated below (Figure 48).

Figure 48: Ruxolitinib, Serious/life-threatening (grade 3-4) adverse reactions

Adverse Reaction	Grade 3-4 Incidence
Infections (type of infection not specified)	41%
Bacterial infections	28%
Haemorrhage (bleeding)	20%
Fatigue	14%
Viral infections	14%
Hypertension (high blood pressure)	13%
Oedema (fluid retention)	13%
Thrombosis (blood clots)	11%
Blood disorders (thrombocytopenia, anaemia, neutropenia)	61%, 45%, 40%

Source: Company presentation

Phase 2 Clinical Study – Ongoing

CYP initiated a phase 2 clinical trial of CYP-001 in high-risk acute GvHD in 2024.

Figure 49: Phase 2 Trial Summary

Product	CYP-001 (Cymerus™ iPSC-derived MSCs for intravenous infusion)
Indication	High risk acute graft versus host disease (aGvHD)[1]
Study Design	• Randomised controlled trial in ~60 adults (steroids + CYP-001 vs steroids + placebo) • Primary objective is to assess efficacy of CYP-001 based on Overall Response Rate at Day 28
Study Conduct	• Clinical sites in USA, Europe and Australia • Regulatory/ethics clearance secured in all participating jurisdictions – including IND from US FDA • First patient enrolled – March 2024 • Aiming to complete patient enrolment by end of calendar year 2024
Results	Primary evaluation results anticipated in 2H CY 2025

Source: company presentation

The study aims to validate the successful phase 1 results in a larger randomised placebo-controlled cohort, which we believe will represents a major de-risking milestone for CYP-001 and potentially accelerate partnering discussions.

The multicentre, randomized, double-blind, placebo-controlled phase 2 study is assessing the safety and efficacy of CYP-001 when administered in combination with corticosteroids versus standalone corticosteroids, as a treatment for high-risk acute GvHD.

In total, CYP will recruit 60 patients with high risk acute GvHD (based on the refined Minnesota Criteria), across ~30 clinical trial sites in the United States, Europe and Australia. Given this is a rare disease, the trial requires a large number of sites per patient recruited (~2 patients per site).

We note, the trial is being run under an approved Investigational New Drug (IND) application from the US FDA for CYP-001.

Once enrolled, patients are randomised into either receiving an IV infusion of CYP-001 (up to a maximum of 200 million cells per infusion) on days 0 and 4 or a placebo on the same days. Alongside this, all patients will receive ongoing corticosteroid therapy, at a minimum dose of oral prednisone 2 mg/kg/day (or methylprednisolone 1.6 mg/kg/day IV) for at least 72 hours post enrolment.

Patients are then monitored in the primary evaluation period up to day 100, with a subsequent follow up period for up to 24 months (2 years).

The study's primary endpoint is the overall response rate (ORR) at day 28.

A range of secondary endpoints are also collected, including safety and tolerability, overall response rate at day 100, overall survival up to 2 years, cumulative weekly steroid dose, and other data points.

Primary evaluation results are anticipated in Late CY2025

High-risk Subgroup Rationale

The rationale for the slight change in indication to high-risk acute GvHD, rather than steroid-resistant acute GvHD as in the Phase 1 study, relates to the recent approval of ruxolitinib for steroid-resistant acute GvHD. While CYP-001's data to date shows far superior efficacy and safety to ruxolitinib, key opinion leaders advised CYP there would be significant recruitment challenges due to the serious, life-threatening nature of steroid-resistant acute GvHD and the ethical difficulties in withholding the only approved treatment in a clinical trial setting.

Therefore, the phase 2 study is being done in patients with newly diagnosed high-risk acute GvHD (based on the refined Minnesota criteria). This avoids the potential recruitment challenges highlighted above, as these patients are not yet eligible to receive ruxolitinib. Moreover, the trial doesn't impact the existing standard of care, as both the treatment and placebo groups receive corticosteroids.

Notably, CYP has hypothesised this trial design, which provides patients with an earlier intervention, could maximise the opportunity for clinical benefits.

Phase 3 Clinical Trial – TBC

We would anticipate a pivotal phase 3 of CYP-001 in high risk acute GvHD, subject to the successful completion of the ongoing phase 2 trial.

This next trial, should it be successful, would enable CYP-001 to secure regulatory approval in the United States, and other key jurisdictions.

We expect this next trial could be initiated in CY 2026, potentially enabling a regulatory filing in CY 2028.

Similar to the ongoing phase 2 trial, we would expect this next study to be a randomised, blinded, placebo-controlled study of CYP-001 in high risk acute GvHD, when administered alongside corticosteroids, albeit in a larger patient cohort.

Moreover, based on the recent approval of ruxolitinib for steroid resistant acute GvHD, we anticipate the primary approvable endpoint will be day 28 overall response rate (ORR).

The phase 3 cohort size will come down to what's expected to be required for the trial to be powered, which will principally be guided by the results of the ongoing phase 2 trial. Indicatively, we wouldn't expect a large trial given the impressive results seen in the phase 1 trial, which implied a large treatment benefit.

Considering all of this, we speculate the trial could costs somewhere in the vicinity of US$30 million to US$50 million.

Furthermore, depending on CYPs partnering strategy, the cost of the trial could ultimately end up being funded by a partner.

Orphan Drug Designation

Acute GvHD is a rare disease and CYP-001 has been granted orphan drug designation in the United States by the FDA.

Orphan drugs come with significant regulatory and commercial incentives, including:

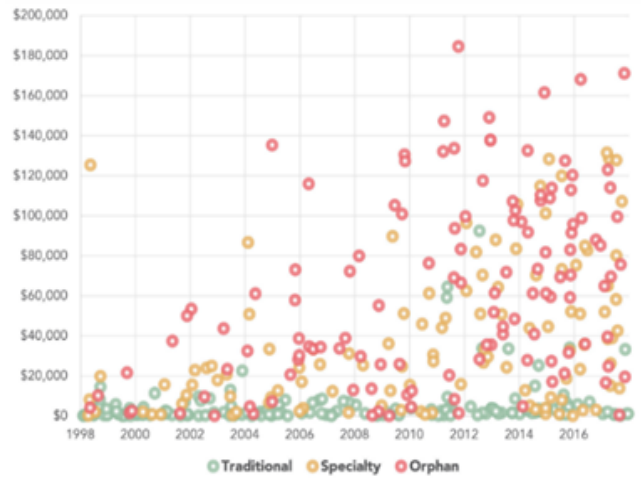
- Reduced fees during the product development phase,
- Protocol assistance from the regulatory authorities; and
- Extended Market exclusivity: 7-years (United States)

The primary benefit of orphan drugs is the commercially attractive pricing. The average annual cost for orphan drug at launch is ~US$123,500 (AHIP, 2019). The higher pricing is a function of the significantly smaller patient populations.

Pricing Benefits

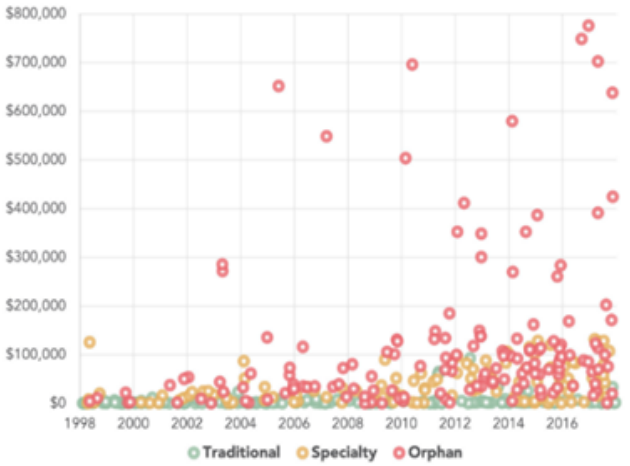
Overlaying this, the market exclusivity period for biologic therapies, such as CYP-001, is even longer at 12 years.

Figure 50: Annual Cost of Drugs at Launch: 1998-2017



Source: AHIP, The Rise of Orphan Drugs

Figure 51: Annual Cost of Drugs at Launch: 1998-2017, Expanded Axis



Source: AHIP, The Rise of Orphan Drugs

CYP-001 Regulatory Pathway

CYP-001 and CYP's other MSC therapies are regulated as the biological products.

To gain regulatory approval in the United States, CYP will need to file and secure a Biologics License Applications (BLA) from the US Food and Drugs Administration (FDA). While largely similar to a New Drug Application (NDA), a BLA review will have a much larger focus on the manufacturing process, as "the product is the process" in cell therapies such as MSCs.

The standard BLA review timeline is 12 months, start to finish, including 2 months to accept the BLA and 10 months to complete the review.

To market in Europe, CYP will need to file and secure a Marketing Authorisation Application (MAA) with the European Medicines Agency (EMA). The assessment process can take up to 210 'active' days (~7 months).

Assuming successful clinical trials, we conservatively estimate CYP-001 would gain regulatory approval in the United States and Europe in 2029 as a treatment for high-risk acute GvHD.

Priority Review Designation

We believe CYP-001 could qualify for FDA priority review status as there remains a significant unmet need in acute GvHD. This would reduce the review time of its BLA from 10 months down to 6 months.

The EMA has a similar pathway known as the Accelerated Assessment Procedure, which reduces the review time frame from 210 days to 150 days.

Regenerative Medicine Advanced Therapy (RMAT) Designation

We believe CYP-001 could be eligible to receive a Regenerative Medicine Advanced Therapy (RMAT) Designation from the US FDA. As previously announced, the agency told CYP it could request the RMAT designation for CYP-001 in the application of acute GvHD.

A RMAT designation would enable CYP to seek priority review and accelerated approval.

CYP-001 Acute GvHD Market Opportunity

We estimate the total addressable market (TAM) for CYP-001 treating high-risk acute GVHD could conservatively be worth +A$1.2 Billion per annum across the United States and Europe.

Figure 52: Estimated Total Addressable Market (TAM), US/EU

	Units	Europe	United States	Combined
Allogeneic HCT Procedures	#	19,000	8,500	27,500
(x) Est Acute GvHD	%	50%	50%	
Acute GvHD	**#**	**9500**	**4250**	**13,750**
(x) Est Steroid Resistant	%	50%	50%	
SR-Acute GvHD	**#**	**4,750**	**2,125**	**6,875**
(x) Assumed Pricing	US$k/pa	100	150	
Est Total Addressable Market	**US$m**	**475**	**319**	**794**
Est Total Addressable Market	**A$m**	**731**	**490**	**1,221**

Source: EH analysis, 0.65 AUD/USD fx

We believe the majority of the CYP-001 market opportunity is centred in the United States and Europe, as the majority of allogeneic HCT procedures and therefore acute GvHD cases occur in these regions.

Estimated Eligible Patient Population

We estimate there are circa ~6,900 annual cases of steroid resistant acute GvHD between the United States and Europe.

This is a conservative estimate of eligible patients, given steroid resistant GvHD would likely be a subset of high-risk acute GvHD, which we believe will be the first approved label indication of CYP-001.

There are circa 27,500 allogeneic HCT procedures annually across the United States and Europe based on data from the Center for International Blood and Marrow Transplant Research and the European Society for Blood and Marrow Transplantation.

Based on the scientific literature, we estimate 50% of patients undergoing allogeneic HCT procedures will go onto develop acute GvHD. Further, we anticipate 50% of those with acute GvHD will progress to a steroid-resistant form of the condition.

Pricing

We estimate CYP-001 will sell for US$150,000 per treatment course in the United States, and US$100,000 per treatment course in Europe.

This price point should be supported by the rare disease status of acute GvHD and the significant unmet need, as evident by the high mortality rate.

Further supporting this estimate, we note relevant therapies have comparable or higher costs:

- Jakafi, the only FDA approved therapy for steroid-resistant acute GvHD, sells for ~US$18,000 per month in the United States. Given an average treatment period is six months, this equates to ~US$108,000 per treatment course.
- Temcell, an MSC therapy approved and marketed in Japan for the treatment of acute GvHD. Sold by Mesoblast's (ASX: MSB) Japanese partner JCR Pharmaceuticals, the therapy costs ~US$7,100 per course of 72 million cells, with the average adult expected to receive between 16 and up to 24 bags of cells. This equates to US$115,000 to US$170,000 per treatment course. Moreover, we note pricing of pharmaceuticals in Japan is traditionally lower than the United States.

Acute GvHD Competitive Landscape

The therapeutic landscape for acute GvHD is relative sparse.

Ruxolitinib is currently the only FDA-approved therapy for steroid resistant acute GvHD. However, Ruxolitinib faces significant shortcomings in both its durable efficacy and safety/tolerability profile, highlighting the need for better treatments.

There are roughly a dozen therapies either in clinical trials or due to begin them.

Figure 53: Acute GvHD Clinical Trials

Drug/Therapy	GvHD Type	Phase	Status	Completion	Comments	NCT Number
Itolizumab	aGVHD	Phase 3	Recruiting	2025	Humanized IgG1 monoclonal antibody	NCT05263999
Obnitix	SR-aGVHD	Phase 3	Recruiting	2027	MSCs; Pooled mononuclear	NCT04629833
MaaT013	SR/Rx-aGVHD	Phase 3	Not recruiting	2025	Allogeneic intestinal microbiota	NCT04769895
RYONCIL (Remestemcel-L)	SR/Rx-aGVHD	Phase 3	Not recruiting	TBD	MSCs; Bone marrow-derived	n/a
Alpha-1 antitrypsin	HR-aGVHD	Phase 3	Not recruiting	2024	Protease inhibitor	NCT04167514
Jaktinib	SR-aGVHD	Phase 2	Not recruiting	2025	JAK inhibitor	NCT04971551
Obnitix	SR-aGVHD	Phase 2	Recruiting	2031	MSCs; Pooled mononuclear	NCT06075706
RLS-0071	SR-GVHD	Phase 2	Recruiting	2025	Dual-targeting Anti-inflammatory Agent	NCT06343792
ASC930	SR-aGVHD	Phase 2	Not recruiting	2026	MSCs; Decidual Placenta-derived	NCT04883918
Cyto-MSC	aGVHD	Phase 1/2	Not recruiting	2025	MSCs; Umbilical cord-derived	NCT03847844
Human Amniotic Epithelial Stem Cells	aGVHD	Phase 1	Not recruiting	2025	MSCs; Placenta-derived	NCT06164288
MSCTC-0010	aGVHD	Phase 1	Recruiting	2025	MSCs; Umbilical cord-derived	NCT03158896

Source: ClinicalTrials.Gov, company announcements, media articles, EH analysis

We discuss key therapies below.

MSC-Therapies (Various)

Over half of these candidates are MSC therapies.

However, all of the MSC therapies listed in the table rely on features of conventional MSC manufacturing – including the requirement of ongoing donors and the use of cell expansion. We believe this will pose significant challenges in their clinical applications, as extensively discussed in this research.

Itolizumab – Equillium (NASDAQ: EQ)

Itolizumab (also referred to as EQ001), is a humanized IgG1 monoclonal antibody.

The drug, in combination with corticosteroids, is currently being evaluated in a randomised, placebo-controlled, phase 3 study (n=200) as a treatment for acute GvHD.

The study's independent data monitoring committee recently completed a blinded interim analysis of the study, reporting no safety or futility concerns and recommending the study proceed as planned.

In a previous phase 1b/2 study (EQUATE, ID: NCT03763318) of patients with grade III-IV acute GvHD (n=22), Itolizumab reported an overall response rate (ORR) of 73% at Day 15 and 68% at Day 29.

The drug has FDA fast-track and orphan drug designation. Equillium has an option agreement with ONO Pharmaceuticals for the asset.

MaaT013 – MaaT Pharma (Euronext Paris: MAAT)

MaaT013 is a donor-derived allogeneic faecal microbiota therapy containing a group of bacterial species known to produce anti-inflammatory short-chain-fatty acids.

MaaT013 is currently being evaluated in a phase 3 study in patients with gastrointestinal acute GvHD, who are refractory to both steroids and Ruxolitinib.

In a previous phase 2a study (HERACLES, NCT03359980) of patients with grade III-IV steroid refractory gastrointestinal acute GvHD, MaaT013 resulted in a 38% gastrointestinal overall response rate at day-28. In a subsequent compassionate use/expanded access program, the gastrointestinal overall response was 58%.

Alpha-1 antitrypsin (AAT) – CSL Behring (ASX: CSL)

Alpha-1 antitrypsin (AAT) is a naturally occurring serine protease inhibitor.

AAT is being evaluated in phase 3 study (n=136) as a treatment alongside corticosteroids in patients with high risk acute GvHD. While the study is listed as active, it is not currently recruiting.

In a prior phase 2 pilot study in patients with steroid resistant acute GvHD, AAT resulted in a 65% overall response at day-28.

Jaktinib – Suzhou Zelgen Biopharmaceuticals (Shanghai: 688266)

Jaktinib is janus kinase inhibitor (JAK inhibitor), similar to Ruxolitinib.

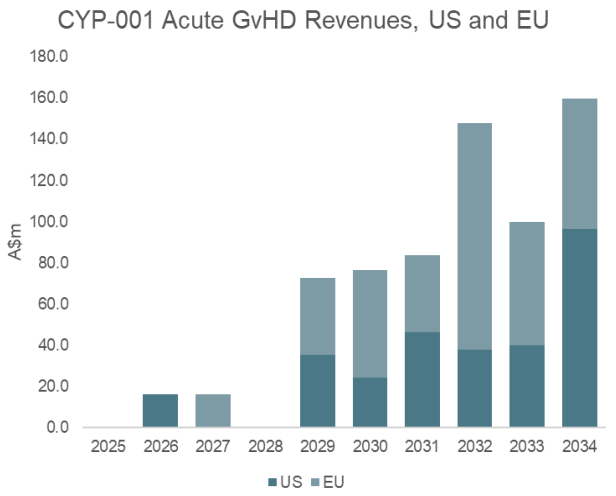
CYP-001 Acute GvHD Forecasts

We have modelled royalty and milestone payment revenues based on CYP-001 being commercialised in acute GvHD across the United States and Europe. This is based on CYP executing two licensing deal, one for each region, following the successful completion of its ongoing Phase 2 clinical trial in high-risk acute GvHD.

Our forecasts are predicated on CYP-001 securing regulatory approval in the United States and Europe as a treatment for high-risk acute GvHD. We believe this will be possible following the success of its ongoing phase 2 clinical trial and a follow-on pivotal phase 3 clinical trial.

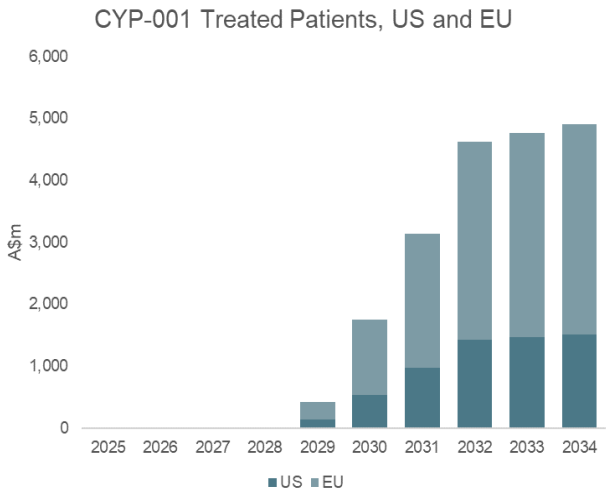
We have segmented our forecasts by region and detailed our key assumptions below.

Figure 54: CYP-001 Acute GvHD Revenues; by Region



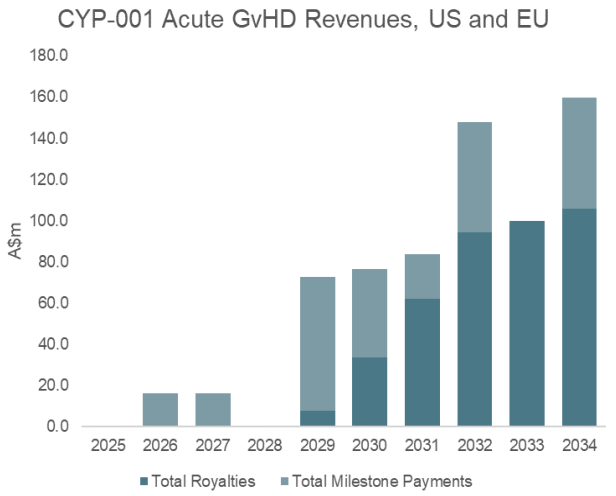
Source: EH analysis, Net of WARF; 0.65 AUD/USD fx

Figure 55: CYP-001 Treated Patients, by Region



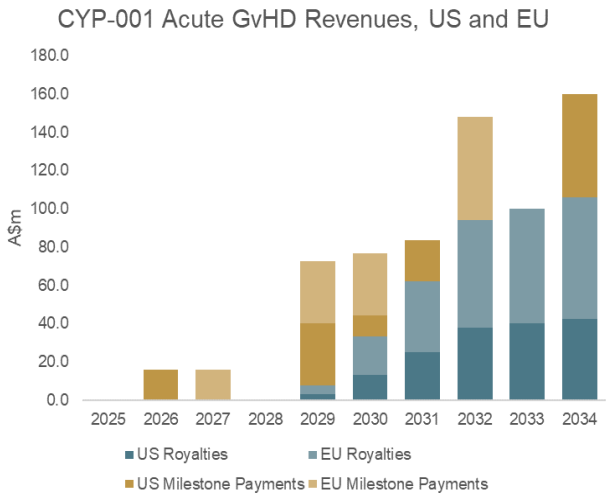
Source: EH analysis

Figure 56: CYP-001 Acute GvHD Revenues; by Type



Source: EH analysis, Net of WARF; 0.65 AUD/USD fx

Figure 57: CYP-001 Acute GvHD Revenues; by Type



Source: EH analysis, Net of WARF; 0.65 AUD/USD fx

Figure 58: USA CYP-001 Acute GvHD Forecasts

Financial Year	Units	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040
United States																	
USA Allo HCT Procedures	'000s	9.3	9.6	9.9	10.1	10.5	10.8	11.1	11.4	11.8	12.1	12.5	12.9	13.2	13.6	14.0	14.5
…Growth	%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%
% with Acute GvHD	'000s	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
% with Steroid Resistant Acute GvHD	'000s	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
Target Patient Population	**'000s**	**2.3**	**2.4**	**2.5**	**2.5**	**2.6**	**2.7**	**2.8**	**2.9**	**2.9**	**3.0**	**3.1**	**3.2**	**3.3**	**3.4**	**3.5**	**3.6**
% market penetration	%					5%	20%	35%	50%	50%	50%	50%	50%	50%	50%	50%	50%
Patients treated with CYP-001	'000s					0.1	0.5	1.0	1.4	1.5	1.5	1.6	1.6	1.7	1.7	1.8	1.8
Pricing	US$'000s					150.0	154.5	159.1	163.9	168.8	173.9	179.1	184.5	190.0	195.7	201.6	207.6
…Growth	%					0%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%
Net Sales	**US$m**	**0.0**	**0.0**	**0.0**	**0.0**	**19.7**	**83.3**	**154.5**	**234.1**	**248.3**	**263.4**	**279.6**	**296.6**	**314.7**	**333.9**	**354.2**	**375.6**
Royalties to CYP	US$m	0.0	0.0	0.0	0.0	2.1	8.7	16.2	24.6	26.1	27.7	29.4	31.1	33.0	35.1	37.2	39.4
Milestone Payments to CYP	US$m	0.0	10.5	0.0	0.0	21.0	7.0	14.0	0.0	0.0	35.0	0.0	0.0	0.0	0.0	0.0	0.0
Total CYP USA Revenues	US$m	0.0	10.5	0.0	0.0	23.1	15.7	30.2	24.6	26.1	62.7	29.4	31.1	33.0	35.1	37.2	39.4
Total CYP USA Revenues	A$m	0.0	16.2	0.0	0.0	35.5	24.2	46.5	37.8	40.1	96.4	45.2	47.9	50.8	53.9	57.2	60.7

Source: EH estimate, 0.65 AUD/USD fx

Key USA CYP-001 Acute GvHD forecast assumptions:

- We assume FDA filing occurs by CY 2028, commercial launch by CY 2029, and a 12-year commercial period (equal to the USA BLA exclusivity period).
- Estimated ~2,200 target patient population, based on quoted number of US allogeneic HCT procedures. Assumes (1) 50% of patients undergoing an allogeneic HCT procedure develop acute GvHD; and (2) 50% of patients with acute GvHD developing steroid resistant version. We assume 3% annual growth in procedures.
- We have assumed 50% peak market share by year 4. Considering Acute GvHD is a rare disease with a significant unmet need, peak market share could be higher and be achieved much sooner. We assume US$150,000 per patient per annum net pricing, escalating by 3% per annum.
- Execution of a US$125m US licensing deal around CY 2026, including a US$15m upfront payment on deal signing and flat 15% royalty on net sales. Our modelled royalties and milestone payment revenues are net of WARF.

Figure 59: EU CYP-001 Acute GvHD Forecasts

Financial Year	Units	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040
Europe																	
EU HCT Procedures	'000s	20.8	21.4	22.0	22.7	23.4	24.1	24.8	25.5	26.3	27.1	27.9	28.8	29.6	30.5	31.4	32.4
…Growth	%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%
% with Acute GvHD	'000s	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
% with Steroid Resistant Acute GvHD	'000s	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
Target Patient Population	**'000s**	**5.2**	**5.3**	**5.5**	**5.7**	**5.8**	**6.0**	**6.2**	**6.4**	**6.6**	**6.8**	**7.0**	**7.2**	**7.4**	**7.6**	**7.9**	**8.1**
% market penetration	%					5%	20%	35%	50%	50%	50%	50%	50%	50%	50%	50%	50%
Patients treated with CYP-001	'000s					0.3	1.2	2.2	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	4.0
Pricing	US$'000s					100.0	103.0	106.1	109.3	112.6	115.9	119.4	123.0	126.7	130.5	134.4	138.4
…Growth	%					0%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%
Net Sales	**US$m**	**0.0**	**0.0**	**0.0**	**0.0**	**29.3**	**124.1**	**230.3**	**349.0**	**370.3**	**392.9**	**416.7**	**442.1**	**469.1**	**497.6**	**527.9**	**560.1**
Royalties to CYP	US$m	0.0	0.0	0.0	0.0	3.1	13.0	24.2	36.6	38.9	41.3	43.8	46.4	49.3	52.3	55.4	58.8
Milestone Payments to CYP	US$m	0.0	0.0	10.5	0.0	21.0	21.0	0.0	35.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total CYP EU Revenues	US$m	0.0	0.0	10.5	0.0	24.1	34.0	24.2	71.6	38.9	41.3	43.8	46.4	49.3	52.3	55.4	58.8
Total CYP EU Revenues	A$m	0.0	0.0	16.2	0.0	37.0	52.4	37.2	110.2	59.8	63.5	67.3	71.4	75.8	80.4	85.3	90.5

Source: EH forecasts, 0.65 AUD/USD fx

Key EU CYP-001 Acute GvHD forecast assumptions:

- We assume EMA filing occurs by CY 2028, commercial launch by CY 2029, and as 12-year commercial period.
- Estimated ~4,800 target patient population, based on quoted number of EU allogeneic HCT procedures. Assumes (1) 50% of patients undergoing an allogeneic HCT procedure develop acute GvHD; and (2) 50% of patients with acute GvHD developing steroid resistant version. We assume 3% annual growth in procedures.
- We assume 50% peak market share by year 4. Considering Acute GvHD is a rare disease with a significant unmet need, peak market share could be higher and be achieved much sooner. We assume US$100,000 per patient per annum net pricing, escalating by 3% per annum.
- Execution of a US$125m EU licensing deal around CY 2027, including a US$15m upfront payment on deal signing and flat 15% royalty on net sales. Our modelled royalties and milestone payment revenues are net of WARF.

Diabetic Foot Ulcer (DFU): CYP-006TK

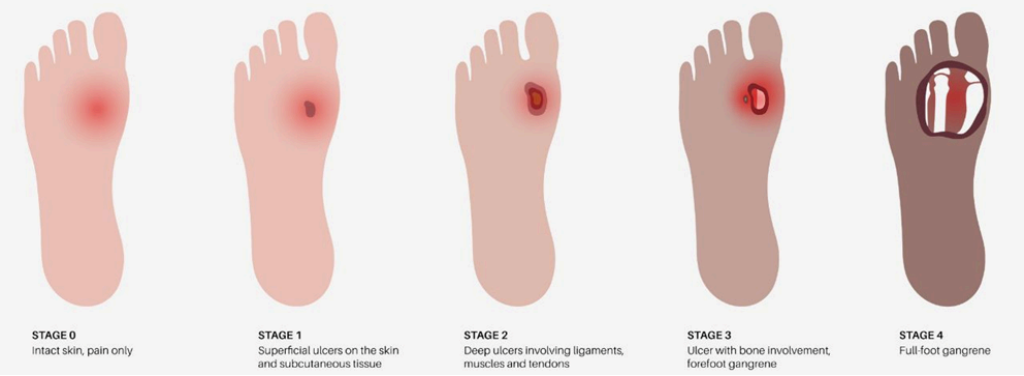
Diabetic Foot Ulcer Overview

Non-healing wounds, particularly in the lower feet/limbs, are a common complication of poorly managed diabetes. These wounds are called diabetic foot ulcers (DFU).

Diabetes is one of the fastest growing chronic diseases, estimated to affect more than 550 million people worldwide (nearly ~1 in 10 people) and 37 million people in the United States alone. Moreover, this number is only expected to grow.

Each year, diabetic foot ulcers affect roughly 18.6 million people worldwide, and 1.6 million in the United States alone. Moreover, up to 34% of people living with diabetes will develop a diabetic foot ulcer at some point in their lives.

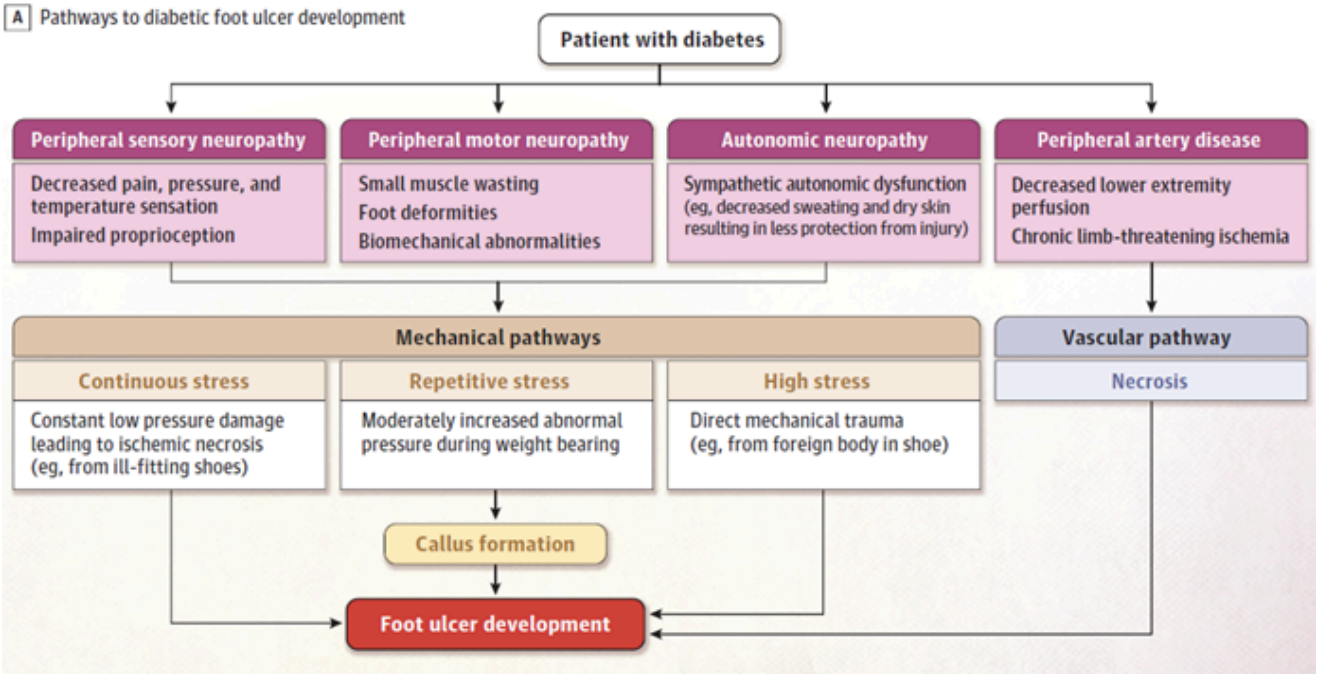
Figure 60: Diabetic Foot Ulcer Staging



Source: RID-IC

Diabetic foot ulcers are a multifaceted disease, typically forming as a result of mechanical stress, enabled by concomitant conditions including nerve damage and poor circulation.

Figure 61: Diabetic Foot Ulcer Development



Source: Diabetic Foot Ulcers, A Review, 2023

Similarly, poorly managed diabetes complicates the healing process of these wounds. If left untreated, diabetic foot ulcers can lead to infection, and in severe cases, result in amputation.

Roughly 50% of diabetic foot ulcers become infected, and up to 20% of these infections require a hospitalisation. Moreover, up to 20% of moderate to severe infections eventually lead to an amputation.

Notably, people with diabetic foot ulcers have a 5-year mortality rate of 30%, which climbs to +70% in patients who require an amputation.

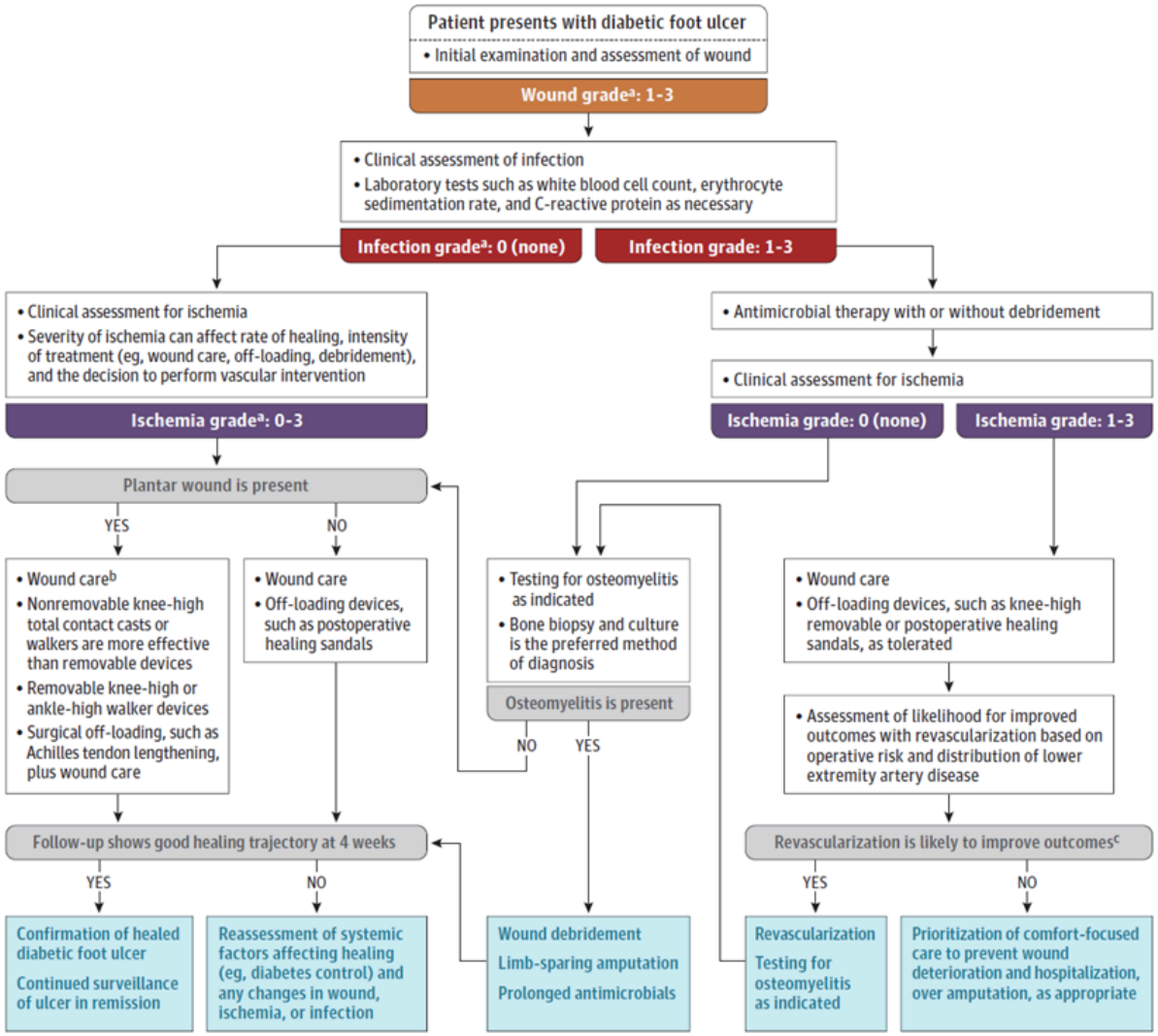
The economic costs are equally significant, with diabetic foot ulcers estimated to result in up to US$13 billion of direct costs in the United States alone.

Standard of Care: New Treatments Needed

Treatment of diabetic foot ulcers requires a multidisciplinary approach (Figure 62) given the multifaceted nature of the condition.

Alongside better management of the underlying diabetes, treatment approaches can include off-loading stress from the wound, debridement (removal) of non-viable wound tissue, and the use of various wound dressings.

Figure 62: Diabetic Foot Ulcer Treatment Algorithm



Source: Diabetic Foot Ulcers, A Review, 2023

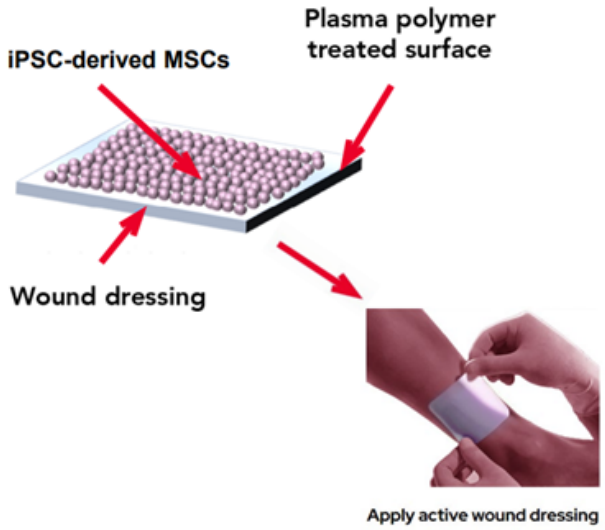
There is limited data on the optimal wound dressing for diabetic foot ulcers, which is further complicated by the selection of dressings ultimately influenced by characteristics of the wound. A wide variety of dressing materials have been studied and are available including hydrogels, hydrocolloids and alginates.

However, the statistics on rates of infection, amputation, as well as related mortality clearly suggest there continues to be an unmet need in patients with diabetic foot ulcers.

CYP-006TK: Potential Second Line (2L) Therapy for DFU

CYP-006TK (Figure 63) is a novel, topical dressing, seeded with iPSC-derived MSCs with the potential to initially be positioned as a second line (2L) therapy for patients with non-healing diabetic foot ulcers.

Figure 63: CYP-006TK Diagram

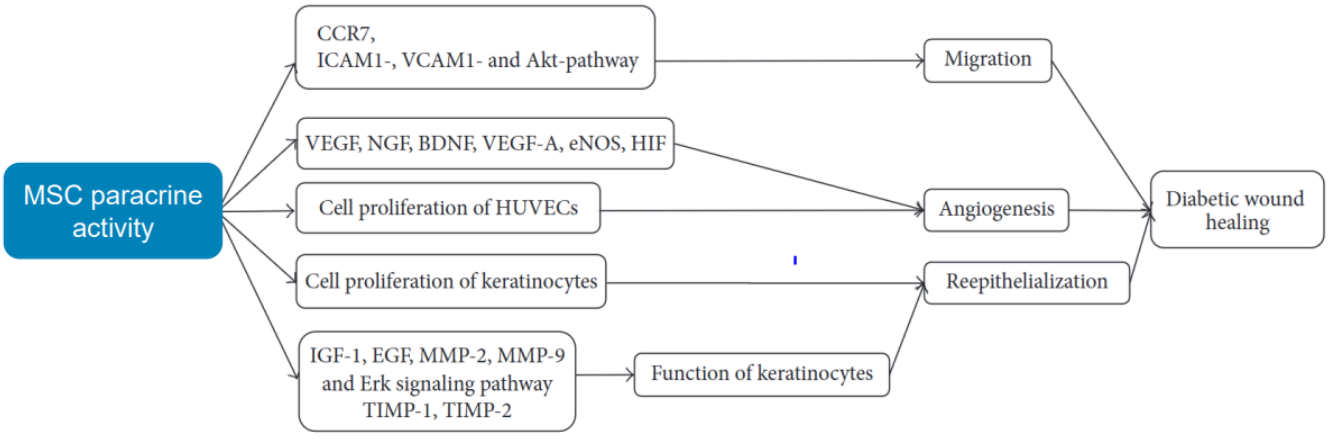


Source: company presentation

CYP-006TK utilises a patented novel silicon dressing, which CYP first licensed from TekCyte, before acquiring the full rights to the technology in 2024.

MSCs have been shown in various studies to facilitate angiogenesis and wound healing. Moreover, MSCs have been shown to possess antimicrobial effects. Overall, this could make MSCs an ideal therapy candidate for diabetic foot ulcers.

Figure 64: Proposed MSC Mechanism of Action in DFU

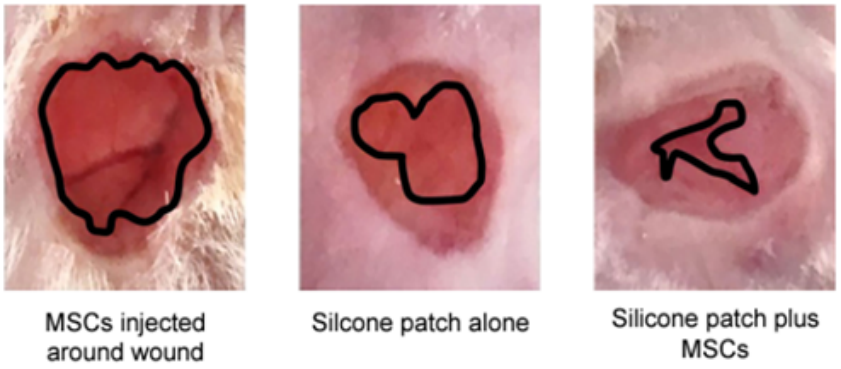


Source: company presentation

Preclinical Studies

Preclinical studies suggest better wound healing is achieved by MSC seeded dressing (silicon patches) versus injecting cells the around the wound, or even just the dressing alone (Figure 65).

Figure 65: Effect of MSC Delivery on Wound Healing



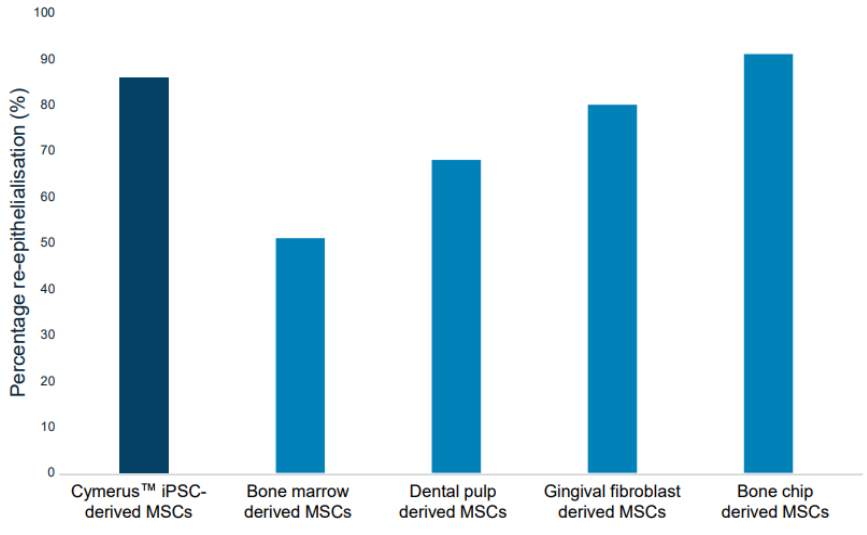
Source: company presentation

Moreover, in a preclinical study comparing MSC's by source through measuring the extent of wound surface healing over 3-days, CYP's iPSC-derived MSCs delivered better wound healing than most other types of donor derived MSCs.

Notably, CYP's iPSC-derived MSC's (86%) reported significantly more surface re-epithelization than bone-marrow derived MSCs (51%), which are the most common type of MSCs used.

While gingival and bone chip derived MSCs were comparable in performance, there is essentially no feasible way to produce a clinical grade product from these sources at scale.

Figure 66: MSC Source Influences Performance



Source: company presentation

Phase 1 Clinical Study

CYP-006TK is currently being evaluated in a multicentre, randomised, controlled phase 1 clinical trial in patients with non-healing diabetic foot ulcers (ID: NCT05165628).

Figure 67: CYP-006TK Phase 1 Trial Overview

Product	CYP-006TK (Novel silicone dressing seeded with Cymerus™ iPSC-derived MSCs)

Study design	• Multi-centre randomised controlled trial, conducted at clinical sites in Australia
	• A total of 30 patients were randomised 1:1 to receive either:
	  • Standard of care treatment (following best practice for the type, severity and stage of ulcer for each participant, at the investigator's discretion); OR
	  • CYP-006TK treatment for 4 weeks (2 applications per week), followed by standard of care treatment
	• Primary objective is safety; efficacy measures include wound healing, pain, quality of life

Study progress	• Patient enrolment complete (April 2024) • Last patient visit expected ~September 2024 • Positive initial results released February 2024 • Final results anticipated in Q4 2024 or Q1 2025

Source: company presentation

The study is fully recruited, with the last of 16 patient visits completed following 24-weeks of treatment. A total of 30 patients were randomised 1:1 into two cohorts:

- CYP-006TK treatment for 4 weeks (2 applications per week); followed by standard of care treatment; or
- Standard of care treatment alone

The study's primary objective is safety, with a number of efficacy measures also collected including wound healing, pain, and overall quality of life.

Earlier this year, CYP provided an early look through into the trial, announcing promising interim results from the first 16 patients after 10 weeks of treatment (8 patients per cohort). These first 8 patients treated with CYP-006TK showed an impressive 87.6% reduction in wound surface area, whereas the patients treated using the standard of care delivered a 51.1% reduction.

Figure 68: CYP-006TK Patient Treatment Example

Source: company presentation

Final results are anticipated in late CY24 or early CY25

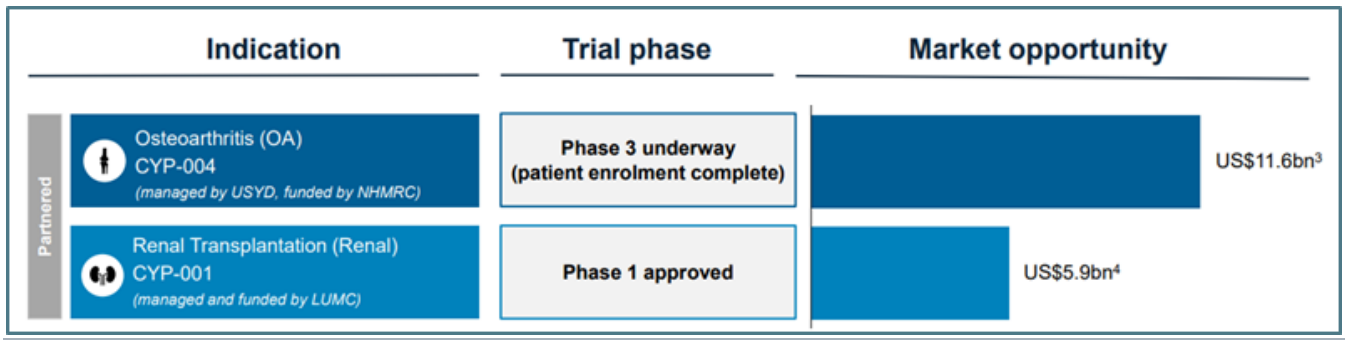
In interpreting these upcoming results, percentage of patients with a complete wound closure is the FDA approvable endpoint, hence clearly an endpoint of focus.

That said, at this stage we are primarily interested in the reduction in wound surface area between cohorts, as this may not be the appropriate trial to form a firm view on complete wound closure. For instance, if CYP were to report positive data on wound surface area reduction but complete closure was not quite achieved, then the company can refine the design of future trials, such as extending the length of treatment, to better evaluate this endpoint.

Investigator Led Programs

CYP's clinical pipeline has investigator led programs (Figure 69) in Osteoarthritis (OA) and Renal Transplantation. These clinical trials are run independent of CYP and require little to no capital contribution.

Figure 69: Investigator Led Programs



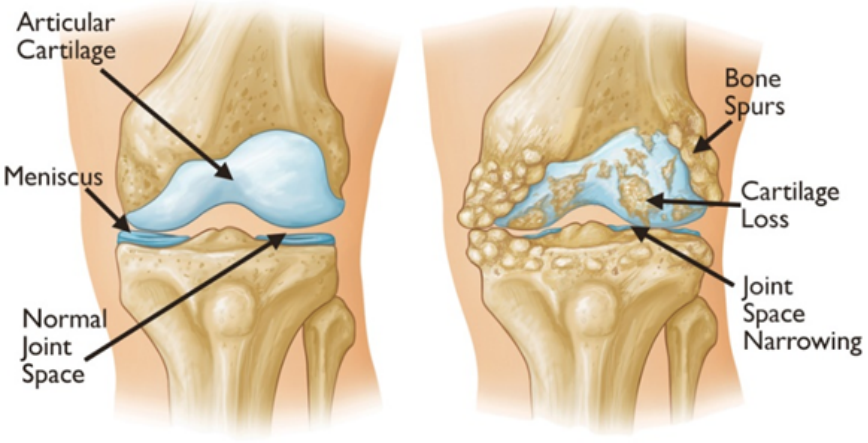
Source: EH analysis, company presentation

Osteoarthritis (OA): CYP-004

CYP-004 is an intra-articular injectable iPSC-derived MSC therapy being developed as a potential treatment to reduce pain, inflammation and cartilage degeneration in patients with Knee Osteoarthritis (KOA).

Osteoarthritis is a chronic degenerative condition of the joints characterised by the degradation of the cartilage (Figure 70).

Figure 70: Knee Osteoarthritis Diagram



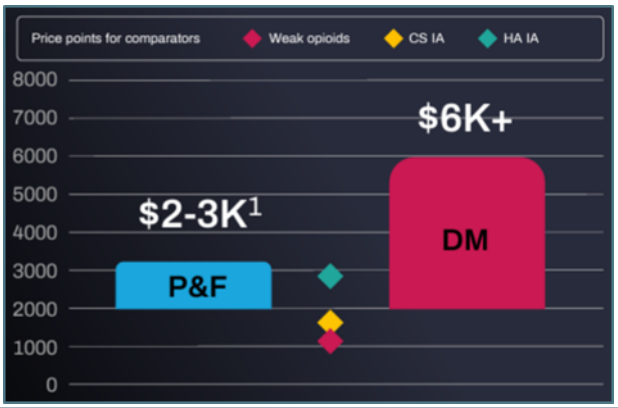
Source: American Academy of Orthopaedic Surgeons

Current treatment options mainly focus on managing the symptoms of osteoarthritis, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroid injections, and even opioids. There are currently no FDA approved disease modifying therapies available for osteoarthritis.

There are an estimated ~33 million adults with osteoarthritis in the United States, according to the Centres for Disease Control (CDC). Globally, there are an estimated +500 million people affected by osteoarthritis.

We note market research conducted on behalf of Paradigm Biopharmaceuticals (ASX: PAR) suggested the price point achievable for a pain and function (P&F) therapy in osteoarthritis was between US$2,000-$3,000 per patient per annum, with achievable pricing estimated to exceed US$6,000 per patient per annum for disease modifying therapies (DM) (Figure 71).

Figure 71: Osteoarthritis Therapy Pricing Market Research

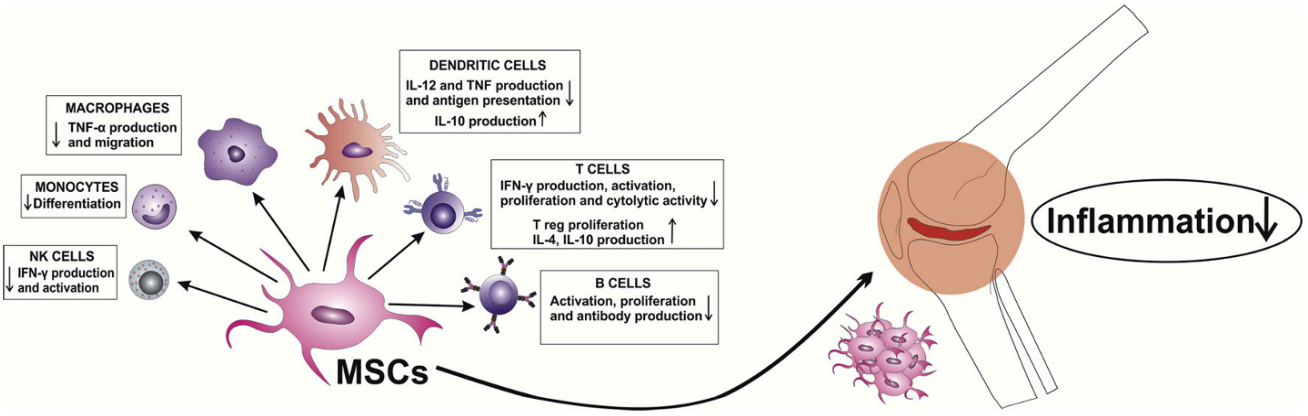


Source: Paradigm Biopharmaceuticals presentation, P&F: Pain and function, DM: Disease modifying

This would suggest a multi-billion-dollar market opportunity for CYP-004 in the treatment of knee osteoarthritis, if demonstrated to work well in even just managing pain and function, let alone the potential if shown to modify the disease.

The pathophysiology of osteoarthritis is complex and may involve immune and inflammatory response processes among other things. This could make MSCs, which have a multifactorial mechanism of action – including immunomodulating and trophic effects (Figure 72) – an ideal therapy candidate for the condition.

Figure 72: Potential MSC Inflammatory Mechanism of Action in Osteoarthritis



Source: C. Randall Harrell, Bojana Simovic Markovic, Crissy Fellabaum, Aleksandar Arsenijevic, Vladislav Volarevic (2019)

A 2018 systematic review of MSC therapies as a treatment for osteoarthritis found that studies supported the idea that MSCs have a positive effect on the condition. However, this review also noted there remained a need for higher-quality and longer-term evidence.

Moreover, we would speculate research generated to date could be limited by the use of conventional donor-derived MSCs. Earlier in this research we touched on the variable results seen in general among clinical studies of MSC therapies. As stated previously, while this remains a debated area, there seems to be broader agreement around the significant limitations with conventional methods of manufacturing MSC's which are thought to contribute to these issues.

Notwithstanding the potential potency and or consistency issues, conventional manufacturing methods would likely face considerable issues in producing enough MSCs to treat a large indication like osteoarthritis – which could potentially require millions of doses.

Whereas CYP's Cymerus manufacturing platform has the capacity to produce a near unlimited amount of MSCs from a single donor. This capability theoretically enables CYP to manufacture CYP-004 in quantities sufficient to support its widespread use as a treatment for osteoarthritis.

CYP-004 is currently being evaluated in a randomised, double-blind, placebo-controlled phase 3 clinical trial, known as SCUlpTOR (Stem Cells as a symptom- and strUcture-modifying Treatment for medial tibiofemoral OsteoaRthritis).

Figure 73: SCUlpTOR Clinical Trial Overview

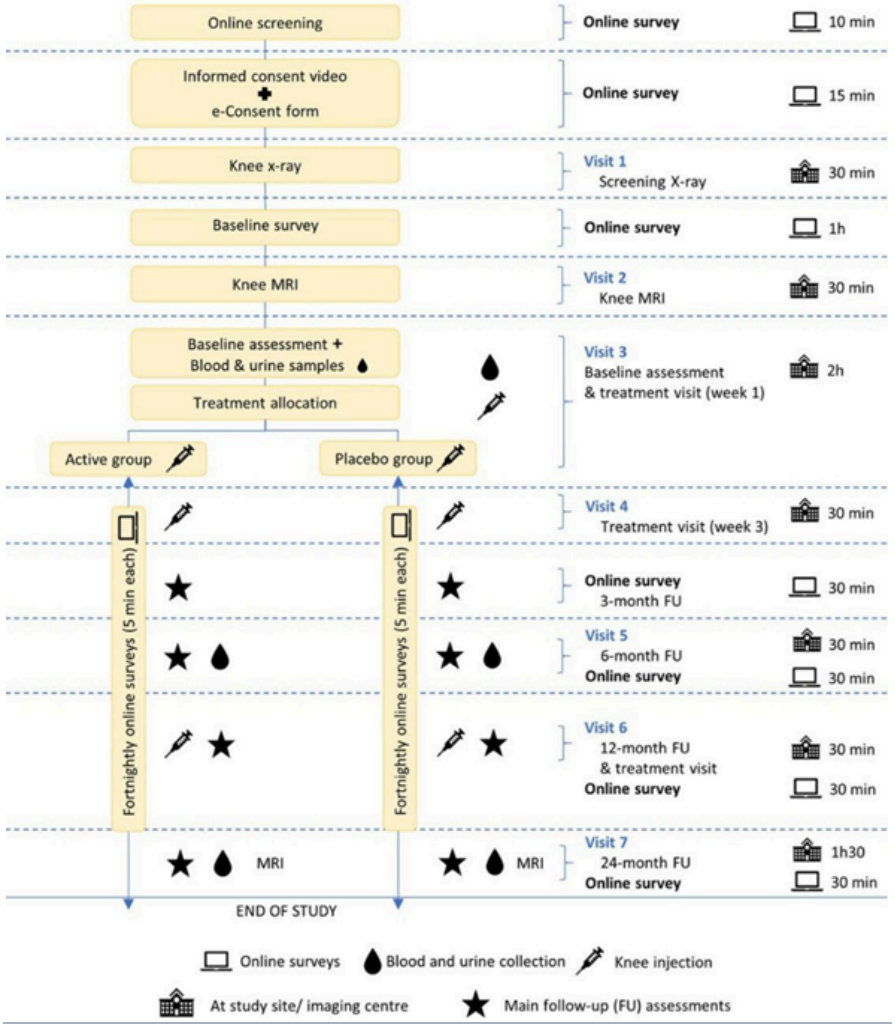
Product	CYP-004 (Cymerus™ iPSC-derived MSCs for intra-articular injection)
Indication	Osteoarthritis (OA) of the knee (Kellgren-Lawrence Grade 2-3)
Study Design	• Randomised, double-blind placebo-controlled trial in ~320 adults • Each participant receives 3 injections over 12 months; follow-up of 24 months from first dose • Co-primary endpoints are reduction of knee symptoms and measure of cartilage loss
Study Conduct	• Trial conducted by University of Sydney, funded by Australian Government NHMRC grant • Clinical centres in Australia (Sydney and Hobart) • Patient enrolment complete (November 2023) • Last patient last visit expected ~November 2025
Results	• Results anticipated in H1 CY 2026

Source: company presentation

While this is a phase 3 study, it is the first human clinical trial of CYP-004 in osteoarthritis.

The trial is being led by Professor David Hunter at the University of Sydney, with grant funding provided by the Australian Government National Health and Medical Research Council (NHMRC).

Figure 74: SCUlpTOR Trial Protocol



Source: Efficacy and cost-effectiveness of Stem Cell injections for symptomatic relief and strUctural improvement in people with Tibiofemoral knee OsteoaRthritis: protocol for a randomised placebo-controlled trial (the SCUlpTOR trial)

Patients will receive 3 courses of intra-articular injection of either CYP-004 or placebo, over a one-year period, with a 2 year follow up period post enrolled. The trial has co-primary endpoints which are:

1. Proportion of participants achieving patient-acceptable symptom state (PASS) for knee pain at 24 months; and
2. Central medial femorotibial (cMFT) cartilage thickness change from baseline to 24 months, as assessed by magnetic resonance imaging (MRI).

Recruitment was completed in November 2023, with a total of 321 patients enrolled.

CYP anticipated the last patient visit (2 years following enrolment) will occur around November 2025, with results in 1H CY26

Kidney Transplantation: CYP-001

In addition to the lead indication of acute GvHD, CYP-001 is being evaluated as a potential immune modulating treatment in patients receiving a kidney transplant.

Patients who receive a kidney transplant will typically require maintenance immunosuppressive therapy post-transplant to prevent organ rejection. This will commonly include the use of calcineurin inhibitors (type of immunosuppressants), which are toxic to the kidneys among other serious side effects.

The multifaceted immune modulating effects of MSCs could makes them a potentially effective candidate in facilitating the reduction or withdrawal of calcineurin inhibitors.

In previous published research, Prof Ton Rabelink and his team (also running the phase 1 trial), showed a patient's own MSCs facilitated a safe early withdrawal from tacrolimus (type of calcineurin inhibitor), without increasing rejection of the transplanted organs.

CYP-001 is being evaluated in an open label, prospective, single-centre phase 1/2b clinical trial in renal transplant patients, with safety being the primary endpoint.

Figure 75: CYP-001 Kidney Transplant Phase 1/2b Study Overview

Product	CYP-001 (Cymerus™ iPSC-derived MSCs for intravenous infusion)
Indication	Prevention of kidney transplant rejection
Study Design	• ~16 patients to receive CYP-001 after kidney transplantation: cohort 1 (n=3); cohort 2 (n=3); cohort 3 (n=10) • Trial will evaluate safety (all cohorts) and efficacy of MSCs in facilitating reduction of calcineurin inhibitors (anti-rejection medication; Cohort 3)

Source: Company presentation

The trial is being run and funded by Leiden University Medical Centre (LUMC) in the Netherlands, under the leadership of Prof Rabelink. CYP is providing CYP-001 drug for the trial, while retaining full rights over the commercial use of the data.

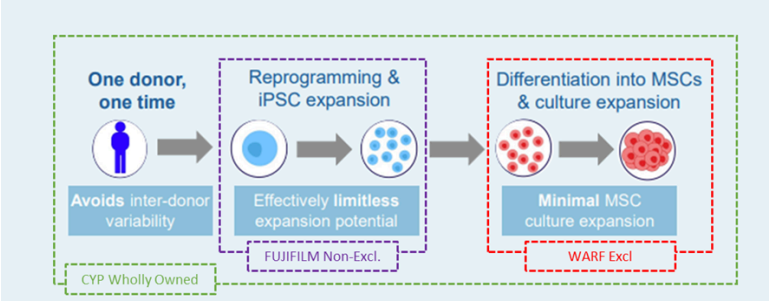
The company recently announced in its September quarterly update the first patient has now been enrolled into the trial, and is expected to be infused with CYP-001 during the current quarter (Q4 CY24).

The trial will recruit up to 16 patients who have had a kidney transplant, with the first 6 patients either receiving one (n=3) or two (n=3) infusions of CYP-001, alongside standard of care. Following a sufficient demonstration of safety in this initial cohort, the following 10 patients will receive two infusions of CYP-001, followed by a reduction in their dosage of tacrolimus (calcineurin inhibitor).

Intellectual Property

CYP maintains a comprehensive intellectual property portfolio comprised of various patent families, both in-licensed and wholly owned by CYP (Figure 76).

Figure 76: CYP Patent Families



Source: EH analysis, CYP

The company's core patents cover key parts of the Cymerus manufacturing technology, and are exclusively licensed from the Wisconsin Alumni Research Foundation (WARF). These include two patent families:

- Generation of Clonal Mesenchymal Progenitors (MCA's) and Mesenchymal Stem Cell (MSCs) Lines under serum-free conditions – Granted, expiring 2028 in the USA, 2031 in the RoW
- Methods and Materials for Hematoendothelial Differentiation (iPSCs to MCAs) of Human Pluripotent Stem Cells Under Defined Conditions – Granted, Expiring 2035 USA, 2034 RoW

Under these exclusive licenses WARF is entitled to an estimated 5% royalty on net sales, in addition to 30% of any upfront or milestone payments CYP receives. There are further minor milestone payments payable by CYP.

It should also be noted having WARF as the licensor provides substantial support to CYP. They represent a very large and well-funded (multibillion-dollar endowment fund) organisation with extensive experience in intellectual property defence. As a result, in the event CYP faces any patent disputes it will be well supported by WARF.

CYP holds additional wholly owned patent families which cover other aspects of the Cymerus manufacturing process, including quality control aspects. These include two patent families:

- Colony forming medium and use thereafter of Cymerus MSC's – Granted, expiring in 2037 in the USA, and 2037 in the RoW.
- Pluripotent stem cell assay – Granted, expiring 2037 in the USA, and 2037 in the RoW.

Notably, these patents are broad in covering any human pluripotent stem cells, which therefore extends to covering human embryonic stem cells (hESC).

CYP has additionally non-exclusively licensed the process of manufacturing iPSCs from FUJIFILM Cellular Dynamics (subsidiary of Fujifilm). While this part of the manufacturing process is non-exclusively licensed, other patents still mean no one can manufacture MSCs from iPSCs without infringing on CYP's intellectual property.

Post approval, CYP could secure a patent extension for select families based on the time in development. This could further extend the patent coverage.

Above all of this, CYP-001 if approved, will be eligible for a considerable period of regulatory market exclusivity as a novel biologic therapy (12-years USA, 10-years EU), which is overlapped by the exclusivity provided through the orphan drug designation (7-years USA, 12-years EU including pediatric extension).

Balance Sheet

CYP had ~$4.3 million in cash at bank as of the September quarter. The company is anticipating its R&D rebate in Q4, which will further supplement the cash balance. CYP currently has no debt.

The company has stated this provides them a forecasted cash runway into 2H CY25.

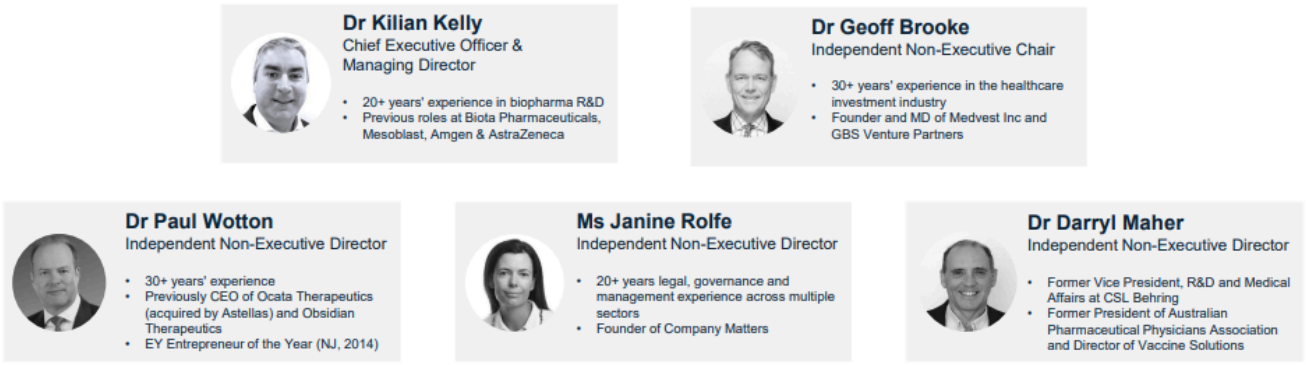
Clearly, given the company remains cash flow negative it will require additional funding at some point in time to progress its clinical programs. This could be facilitated through licensing agreements, equity capital, debt, or a mix of all.

Board and Management

Board of Directors

We outline CYP's board of directors below.

Figure 77: Board of directors



Source: company presentation

Dr Kilian Kelly – Chief Executive Officer and Managing Director

Shares / options: 0.6m; 2.8m

Background: Dr Kilian Kelly has over 20 years' experience in biopharmaceutical research and development, including more than 13 years focussed on development of mesenchymal stem (MSC) based therapies. He joined Cynata in March 2014, initially as Vice President, Product Development, then acted as Chief Operating Officer from May 2019, before taking on the role of CEO & MD in July 2023. At Cynata, he has overseen all stages of the development of the Cymerus™ iPSC-derived MSC technology, including the first completed clinical trial of any iPSC-derived product worldwide.

Dr Kelly previously held positions at Biota Pharmaceuticals, Mesoblast Limited, Kendle International, Amgen and AstraZeneca. He holds a Masters in Pharmacy degree from the Robert Gordon University, Aberdeen and a PhD in Pharmaceutical Sciences from Strathclyde University, Glasgow. He is a graduate and member of the Australian Institute of Company Directors (AICD), and a member of the International Society for Cell and Gene Therapy (ISCT), the International Society for Stem Cell Research (ISSCR) and the Royal Pharmaceutical Society. He also currently serves on the ISCT Asia-Pacific Industry Committee, the ISSCR Best Practices Regulatory Working Group and the Industry Interface Committee of the Center for Commercialisation of Regenerative Medicine (CCRM) Australia.

Dr Geoff Brooke – Independent Non-Executive Chairman

Shares / options: 0.3m; 2.6m

Background: Dr Brooke joined the Cynata Board in May 2019 as Non-Executive Director, and was subsequently appointed Chair in August 2020. He has more than 30 years' venture capital experience, including co-founding GBS Venture Partners in 1996 and serving as 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. Additionally, from 2009 until 2015, he was an Independent Director of the Victoria Workcover Authority. Dr Brooke currently serves on the Boards of two other public companies, as Chair of Actinogen Medical Limited (ASX: ACW), and Non-Executive Director of Acrux Limited (ASX:ACR). He also works with a number of other entities, including as a consultant to BioScience Managers. Dr Brooke holds a Bachelor of Medicine/Surgery from Melbourne University and a Masters of Business Administration from IMEDE (now IMD) in Switzerland.

Dr Paul Wotton – Independent Director

Shares / Options: 0.3m; 0.6m

Background: Dr. Wotton joined Cynata's Board of Directors in June, 2016. He is Executive Chairman of the Biotech LaunchPad at Rice University, Houston. He was President and CEO of Obsidian Therapeutics, Founding CEO of Sigilon Therapeutics (Acquired by Lilly) and President and CEO Ocata Therapeutics, Inc. (NASDAQ: OCAT) which was acquired by Astellas in 2016. Prior to Ocata, Dr. Wotton had served as President and CEO of Antares Pharma Inc. (NASDAQ: ATRS). Prior to joining Antares, Dr. Wotton was the CEO of Topigen Pharmaceuticals. Earlier in his career he held senior level executive positions at SkyePharma plc, Eurand International BV, Penwest Pharmaceuticals, Abbott Laboratories and Merck, Sharp and Dohme. Dr. Wotton is a member of the board of Vericel Corporation (NASDAQ:VCEL), Chairman of Dimension Inx., and Chairman of Kytopen Inc. Dr. Wotton received his Ph.D. in pharmaceutical sciences from the University of Nottingham. In 2014 he was named EY Entrepreneur of the Year (NJ) in Life Sciences.

Ms Janine Rolfe – Independent Director

Shares / Options: 0.1m; 0.6m

Background: Ms Rolfe joined the Cynata Board in September 2022 and brings over two decades' of legal, governance and management experience across multiple sectors, including highly regulated industries and complex global businesses. Before recently transitioning as a professional non-executive director, Janine's last executive position was General Counsel & Company Secretary of Link Administration Holdings Limited (Link Group). Prior to that, Janine founded Company Matters Pty Limited and worked both in-house (Qantas Airways Limited) and in private practice (Mallesons Stephen Jaques, now King & Wood Mallesons), across a diverse and distinguished career. Janine is an Independent Non-Executive Director of Cloudwerx Holdings Pty Limited and a Board Member of the Independent Liquor & Gaming Authority, NSW Government. Janine has held a number of Board positions in the past including with Property Exchange Australia Limited (PEXA), the Qantas Foundation Trustee, and Bothar Boring Pty Limited. Janine is a member of the Australian Institute of Company Directors (AICD) and received a Bachelor of Economics and Bachelor of Laws (Honours) from the University of Sydney.

Dr Darryl Maher – Independent Director

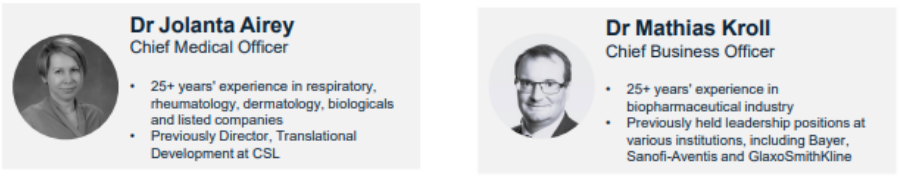
Shares / Options: 0.1m; 0.6m

Background: Dr Maher joined the Cynata Board in June 2020 following over 20 years in the pharmaceutical industry as a senior R&D Executive at CSL Limited. His most recent position was 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 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. He was a former President of the Australian Pharmaceutical Physicians Association and a director of Vaccine Solutions. He earned his Bachelor of Medicine/Surgery from the University of Melbourne, Australia and undertook his PhD at The Walter and Eliza Hall Institute of Medical Research. He is a retired Fellow of both the Royal Australian College of Physicians and the Royal College of Pathologists of Australia.

Executive Team

We outline key members of CYP's executive team below.

Figure 78: Key executive team members



Source: company presentation

Dr Mathias Kroll – Chief Business Officer

Background: Dr Mathias Kroll has over 25 years' experience in biopharmaceutical research and business development. He joined the Company in April 2024 as Chief Business Officer. Dr. Kroll has extensive global experience in biopharmaceutical business transactions of all kinds and has created and managed a large number of partnerships ranging in value up to several billion dollars.

His previous appointments are Chief Commercial Officer, QIMR Berghofer (AUS), Chief Executive Officer, InProTher ApS (DK, now Hervolution Therapeutics), Global Head of Business Development, Bavarian Nordic (DK), Sr Director Global Business Development, GlaxoSmithKline Vaccines (BE), Assoc. Product Director and Global Brand Manager, UCB (BE), Assoc. Director Business Development, UCB Japan (JP), Research Unit Head, Sanofi (FR), Laboratory Head, Bayer Healthcare (DE), Vis. Assoc. Consultant, Boston Consulting Group (DE), and Research Associate, INSERM (FR). Following studies and research work performed at the Universities of Dusseldorf (DE), Paris (FR), North Carolina at Chapel Hill (USA), and at IMD in Lausanne (CH), Dr Kroll holds Master's degrees in Chemistry, Biology, and Business Administration, a diploma in Molecular Virology, and a PhD in Viral Immunology for work performed at Pasteur Institute (FR). He is a member of the Australian Institute of Company Directors. He also served on the Selection Panel of CUREator, Australia's national biotech incubator.

Dr Jolanta Airey – Chief Medical Officer

Description: Dr Airey is an accomplished biopharmaceutical executive and physician with broad international experience in the successful development and commercialisation of pharmaceutical products including novel biological agents. She has been involved in the design and execution of multiple clinical trials from early through to late stage, encompassing a wide range of therapeutic categories in multiple geographies. Dr Airey joined Cynata in October 2021 from CSL Limited, where she was Director, Translational Development. Prior to CSL, Dr Airey was a Clinical Development Physician at Seqirus, a CSL company, and earlier held a range of medical positions within biotech, pharmaceutical and clinical research companies. Her career path has led to her playing important roles in the market approvals of several drug products.

Scientific Advisors

CYP has scientific advisors which it engages for guidance on the company's research and development programs. These advisors are shown below.

Professor Igor Slukvin

Background: Igor Slukvin is Professor of Pathology and Laboratory Medicine at the University of Wisconsin-Madison, School of Medicine and Public Health. His research program focuses on development of hematopoietic, vascular and mesenchymal lineages from human pluripotent stem cells. His work identified several novel progenitors for blood, endothelial and mesenchymal stem cells, including mesenchymoangioblasts (MCAs), a common precursor for endothelial and mesenchymal stem cells.

Professor Slukvin received his MD and PhD from Kiev Medical University, Ukraine, and completed postdoctoral and medical residency training at the University of Wisconsin. He has published over 70 peer reviewed research papers and serves on several editorial boards.

Professor Slukvin holds key patents in the area of haematovascular cell production from human pluripotent stem cells, several of which form the core of the Company's intellectual property portfolio, and is a co-founder of Cynata and also of Cellular Dynamics International, previously listed on Nasdaq but acquired by FUJIFILM in 2015 for US$307m.

Professor Chrishan Samuel

Background: Chrishan Samuel is Head of the Fibrosis Laboratory and Deputy Head (Research) of the Department of Pharmacology at Monash University, and is also the Deputy Head of the Cardiovascular Disease Program within the Monash Biomedicine Discovery Institute. His research program focuses on the development and evaluation of novel peptide, stem cell and combination therapies/strategies for treating organ fibrosis (scar tissue accumulation), which is a hallmark of organ failure.

Professor Samuel received his PhD from the University of Melbourne, completed his post-doctoral training at the Stanford University School of Medicine and Molecular Medicine Research Institute (CA, USA) and then the Howard Florey Institute (University of Melbourne), before joining Monash University in 2012. He has authored over 160 publications and serves on several editorial boards and committees.

Since 2016, Professor Samuel has consulted to and worked with Cynata Therapeutics to develop their CymerusTM-derived MSCs as a potential treatment for respiratory diseases associated with fibrosis, including asthma and idiopathic pulmonary fibrosis.

Top Shareholders

The top shareholders as provided in the annual report are shown below (Figure 79).

Figure 79: Top 20 Shareholders

Name	Shares Held	Issued Capital
	No.	%
Phillip Asset Management Limited <Bioscience MTF1 A/C>	23,588,040	13.06
HSBC Custody Nominees (Australia) Limited	14,731,445	8.16
Fujifilm Corporation	8,088,403	4.48
Citicorp Nominees Pty Limited	6,591,672	3.65
BNP Paribas Nominees Pty Ltd <IB AU Noms Retailclient>	4,323,767	2.39
Kenneth Adrian Raymond Wilson	3,549,905	1.97
BNP Paribas Nominees Pty Ltd <Clearstream>	3,039,266	1.68
Mrs Aily Lamb	2,360,000	1.31
J P Morgan Nominees Australia Pty Limited	2,025,850	1.12
Dr Ross Alexander Macdonald	2,000,000	1.11
National Nominees Limited	1,780,000	0.99
Mr Craig Lawrence Darby	1,729,477	0.96
BNP Paribas Noms Pty Ltd	1,684,988	0.93
Mal Washer Nominees Pty Ltd <Mal Washer Family A/C>	1,559,534	0.86
Mr Pawel Rej & Mrs Miroslawa Rej	1,543,036	0.85
Crosswind Trustee Company Limited <Crosswind A/C>	1,513,000	0.84
Mr Patrick Anthony Walsh	1,341,790	0.74
Souttar Superannuation Pty Ltd <Greenslade Super Fund A/C>	1,330,000	0.74
Mr Jon Nicolai Bjarnason & Mrs Rina Eghoje Bjarnason <Jarck Super Fund A/C>	1,311,034	0.73
Dr Maksym Vodyanyk	1,191,658	0.66
	85,282,865	**47.23**

Source: 2024 Annual report

We note the register includes notable larger shareholders (per a recent investor presentation & the annual report) including:

- Bioscience Managers, speciality healthcare investment fund – 13%;
- Fidelity International, major asset management firm – 10%
- Fujifilm Corporation – 4.5%

Company disclosures

The companies and securities mentioned in this report, include:

Cynata Therapeutics Ltd (CYP)*;

Price, target price and rating as at 06 November 2024 (not covered)*

Additional disclosures

Euroz Hartleys declares that it has provided corporate advice during the last year and has received a fee for these services from: Cynata Therapeutics Ltd (CYP)

Euroz Hartleys has received an allocation of shares and/or options as part of our fee for the provision of Corporate services. These holdings are maintained in our Nominee company, and may present a potential benefit to Euroz Hartleys when sold for: Cynata Therapeutics Ltd (CYP)

Other disclosures, disclaimers and certificates

Copyright & Distribution

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