

5 March 2024

## More shots on goal – new blood cancer indication for SNT-5505

### NEED TO KNOW

- New Phase 2 clinical trial of SNT-5505 in MDS – a condition with high unmet need for new treatments
- SNT-5505 combination trial recruits first patient in MF

**Syntara adds Phase 2 clinical trial in myelodysplastic syndrome (MDS):** Syntara (previously known as Pharmaxis) has announced a new Phase 2 clinical trial evaluating SNT-5505 + chemo combination treatment in patients with low and intermediate risk myelodysplastic syndrome (MDS), a new indication. Syntara will provide \$700K over the anticipated 3-year duration of the study's dose escalation and expansion phases, supply the study drug and perform LOX assays on tissue samples. MDS is a diverse group of blood disorders which lead to problems in making blood cells effectively, and patients have a higher chance of developing acute myeloid leukemia. While many patients have lower-risk MDS that is managed by existing treatments, the treatments are generally not curative and relapse rates are high. No uniform standard of care exists for many patients.

**Phase 2 trial of SNT-5505 + ruxolitinib in myelofibrosis (MF) recruits first patient:** This key trial for Syntara's primary drug development initiative + JAK inhibitor ruxolitinib (standard of care) will expand the current monotherapy trial. 15 patients who now take ruxolitinib will receive ruxolitinib + SNT-5505 for 52 weeks. Syntara expects to render interim results in 2HCY24.

### Investment Thesis

**Overall focus on dysfunction of the extracellular matrix (ECM), a key element in many diseases with high unmet need:** The ECM is a network of fibres, collagen and other proteins that link cells to form tissues; it also provides key signals to cells and regulates the movement of molecules between them. Syntara is working to develop powerful inhibitors of enzymes that affect the ECM, using amine oxidase chemistry and other technologies, in order to develop new medicines for blood cancers and inflammatory and fibrosis-related conditions. Many of these diseases have high unmet need.

**Deep clinical pipeline:** Syntara's most advanced clinical asset, SNT-5505, is in Phase 2 clinical trials for primary MF (a rare bone marrow cancer involving fibrosis) and will begin Phase 2 for MDS later in 2024. SNT-5505 is a novel small molecule and irreversible inhibitor to key enzymes involved in forming collagen, specifically the lysyl oxidase (LOX) family of proteins, whose overproduction is implicated in many conditions of chronic inflammation and pathological fibrosis.

**Lots of results coming in the foreseeable future:** The recent addition of the MDS trial means that Syntara is now conducting four Phase 2 trials; thus, the next 18 months should see strong newsflow from the trial results.

### Valuation

We value Syntara at A\$234m, or A\$0.20 (previously A\$0.33) per share on a fully diluted basis, using a risk-adjusted NPV-based SOTP (sum-of-the-parts) approach. This comprises the four clinical programs (SNT-5505 in MF, SNT-5505 in MDS, SNT-6302, SNT-4728) and an 8-year royalty stream from the divested mannitol respiratory business. The lower share price is largely the result of increased shares on issue post capital raise.

### Risks

Our valuation is most sensitive to clinical risk associated with the SNT-5505 and SNT-6302 programs at this point.

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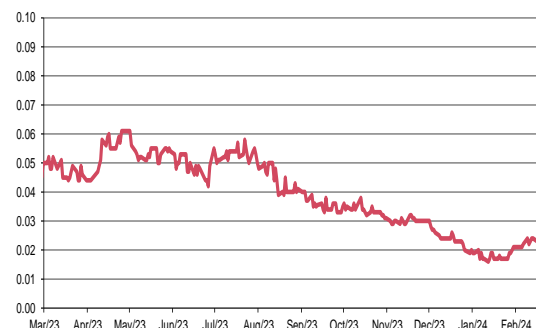
Syntara (previously known as Pharmaxis) is a clinical-stage drug discovery company targeting extracellular matrix (ECM) dysfunction with its world-leading expertise in amine oxidase chemistry, and mechanism-based inhibitors of amine oxidases, to develop novel medicines for blood cancers and conditions linked to inflammation and fibrosis. Currently active clinical programs are focused on a subset of oxidase enzymes known as lysyl oxidases, thought to be responsible for the development of fibrosis by cross-linking collagen and elastin, resulting in hardened, poorly degradable scar-like tissue. Syntara has active clinical programs in the three therapeutic areas of cancer, skin scarring and neurodegenerative disease.

Valuation	<b>A\$0.20</b> (prev. A\$0.33)
Current price	<b>A\$0.02</b>
Market cap	<b>A\$27m</b>
Cash on hand	<b>A\$5.69m</b> (31 Dec 2023)

### Upcoming Catalysts/Newsflow

Period	
1QCY24	SNT-6302: scarring program, expecting first patient
2HCY24	SNT-5505: interim 6-month data of Phase 2 myelofibrosis (MF) trial (combination w/ standard of care)
4QCY24	SNT-5505 Phase 2 trial in MDS, expecting first patient
1HCY25	SNT-4728: neurodegenerative disease Phase 2 trial results

### Share Price (A\$)



Source: FactSet, MST Access.

# Financial Summary

Syntara						SNT-AU
Year end 30 June, AUD unless otherwise noted						
MARKET DATA						
Price	\$	0.02				
52 week high / low	\$	0.02-0.06				
Valuation	\$	0.20				
Market capitalisation	\$m	27.4				
Shares on issue (basic)	m	1191.4				
Options / rights	m	45.5 - includes directors options				
Other equity	m	0.0				
Shares on issue (diluted)	m	1236.9				
12-MONTH SHARE PRICE PERFORMANCE (A\$)						
INVESTMENT FUNDAMENTALS						
		FY22A	FY23A	FY24E	FY25E	FY26E
Reported NPAT	\$m	(1.9)	(11.4)	(8.2)	(13.3)	(4.5)
Underlying NPAT	\$m	(1.9)	(11.4)	(8.2)	(13.3)	(4.5)
Reported EPS (diluted)	c	(0.3)	(1.7)	(1.1)	(0.9)	(0.3)
Underlying EPS (diluted)	c	(0.3)	(1.7)	(1.1)	(0.9)	(0.3)
Growth	%					
Underlying PER	x	nm	nm	nm	nm	nm
Operating cash flow per share	c	(3.0)	(1.0)	(0.5)	(0.7)	(0.3)
Free cash flow per share	c	(3.0)	(1.0)	(0.5)	(0.7)	(0.3)
Price to free cash flow per share	x	nm	nm	nm	nm	nm
FCF Yield	%	nm	nm	nm	nm	nm
Dividend	c	0.0	0.0	0.0	0.0	0.0
Payout	%	0.0%	0.0%	0.0%	0.0%	0.0%
Yield	%	0.0%	0.0%	0.0%	0.0%	0.0%
Franking	%	0.0%	0.0%	0.0%	0.0%	0.0%
Enterprise value	\$m	22.8	22.8	20.2	18.2	23.9
EV/EBITDA	x	(1.8)	(2.4)	(2.6)	(1.4)	(5.9)
EV/EBIT	x	(1.5)	(2.0)	(2.5)	(1.4)	(5.5)
Price to book (NAV)	x	1.2	1.7	2.1	7.1	424.7
Price to NTA	x	1.3	1.9	2.2	8.1	(86.0)
KEY RATIOS						
		FY22A	FY23A	FY24E	FY25E	FY26E
EBITDA margin	%	nm	nm	nm	nm	nm
EBIT margin	%	nm	nm	nm	nm	nm
NPAT margin	%	nm	nm	nm	nm	nm
ROE	%	nm	nm	nm	nm	nm
ROA	%	nm	nm	nm	nm	nm
Net tangible assets per share	\$	0.0	0.0	0.0	0.0	(0.0)
Book value per share	\$	0.0	0.0	0.0	0.0	0.0
Net debt/(cash)	\$m	(4.6)	(4.6)	(7.2)	(9.2)	(3.5)
Interest cover (EBIT/net interest)	x	nm	nm	nm	nm	nm
Gearing (net debt/EBITDA)	x	nm	nm	nm	nm	nm
Leverage (net debt/(net debt + equity))	x	nm	nm	nm	nm	nm
DUPONT ANALYSIS						
		FY22A	FY23A	FY24E	FY25E	FY26E
Net Profit Margin	%	nm	nm	nm	nm	nm
Asset Turnover	x	0.3	0.2	0.3	0.0	0.0
Return on Assets	%	nm	nm	nm	nm	nm
Financial Leverage	x	397.1	448.8	159.7	450.6	26,776.2
Return on Equity	%	nm	nm	nm	nm	nm
KEY PERFORMANCE INDICATORS						
		FY22A	FY23A	FY24E	FY25E	FY26E
<b>Clinical development pipeline</b>	<b>Indication</b>					<b>Status</b>
SNT-5505	Myelofibrosis					Phase 2a
SNT-5505	Myelodysplastic syndrome					Phase 2
SNT-6302	Keloid scarring					Phase 2 ready
SNT-4728	isolated REM Sleep Behaviour Disorder (iRBD)					Phase 2
HALF YEARLY DATA						
		2H21	1H22	2H22	1H23	2H23
Total Revenue	\$m	9.9	8.5	1.6	9.2	10.0
Operating expenses	\$m	(11.3)	(15.6)	(12.5)	(12.6)	(16.0)
EBITDA	\$m	(1.4)	(7.1)	(10.9)	(3.4)	(6.0)
EBIT	\$m	(1.4)	(8.6)	(12.4)	(4.8)	(6.5)
PBT	\$m	(3.0)	(8.8)	1.3	(4.9)	(6.6)
Reported NPAT	\$m	(3.0)	(8.8)	1.3	(4.9)	(6.6)
PROFIT AND LOSS *						
		FY22A	FY23A	FY24E	FY25E	FY26E
Revenue	\$m	7.4	5.8	6.1	0.0	0.0
Other income	\$m	8.3	13.4	5.5	3.6	4.5
Total Revenue	\$m	15.8	19.2	11.6	3.6	4.5
Operating expenses	\$m	(28.1)	(28.6)	(19.3)	(16.4)	(8.5)
EBITDA	\$m	(12.3)	(9.4)	(7.7)	(12.8)	(4.0)
Depreciation & Amortisation	\$m	(3.2)	(1.8)	(0.5)	(0.4)	(0.4)
EBIT	\$m	(15.5)	(11.3)	(8.1)	(13.2)	(4.4)
Net interest	\$m	0.2	0.1	0.0	0.0	0.0
Pretax Profit	\$m	(1.9)	(11.4)	(8.2)	(13.3)	(4.5)
Tax expense	\$m	0.0	0.0	0.0	0.0	0.0
Reported NPAT	\$m	(1.9)	(11.4)	(8.2)	(13.3)	(4.5)
Shares on issue	m	549.1	722.1	1,191.4	1,408.8	1,408.8
GROWTH PROFILE						
		FY22A	FY23A	FY24E	FY25E	FY26E
Revenue	%	(33.3)	21.8	(39.6)	(69.0)	24.2
EBITDA	%	(2,557.1)	(23.6)	(18.6)	67.0	(68.6)
EBIT	%	486.5	(27.6)	(27.9)	62.5	(66.9)
Reported NPAT	%	(34.8)	486.8	(28.1)	62.2	(66.4)
DPS	%	nm	nm	nm	nm	nm
BALANCE SHEET						
		FY22A	FY23A	FY24E	FY25E	FY26E
Cash	\$m	8.9	9.2	11.3	5.6	1.0
Receivables	\$m	8.0	7.8	2.7	0.0	0.0
Other	\$m	2.3	1.6	3.3	0.0	0.0
Current assets	\$m	19.2	18.7	17.3	5.6	1.0
PPE	\$m	3.2	1.8	1.6	1.4	1.3
Intangible assets	\$m	1.0	0.7	0.6	0.5	0.5
Other	\$m	1.7	2.8	2.8	2.8	2.8
Non current assets	\$m	6.0	5.3	5.0	4.8	4.6
Total assets	\$m	25.2	24.0	22.3	10.3	5.6
Trade and other payables	\$m	2.7	4.7	3.4	0.0	0.0
Borrowing	\$m	2.0	2.0	2.0	2.0	2.0
Other	\$m	1.4	1.3	1.3	1.3	1.3
Current liabilities	\$m	6.1	8.0	6.7	3.3	3.3
Borrowing and leases	\$m	2.3	0.0	0.0	0.0	0.0
Other liability	\$m	6.0	6.4	2.8	2.5	2.2
Non current liabilities	\$m	8.3	6.4	2.8	2.5	2.2
Total liabilities	\$m	14.4	14.5	9.5	5.8	5.5
Net assets	\$m	10.8	9.6	12.8	4.5	0.1
Share capital	\$m	380.4	389.7	401.1	406.1	406.1
Retained earnings	\$m	(393.1)	(404.5)	(412.6)	(425.9)	(430.3)
Other	\$m	23.5	24.3	24.3	24.3	24.3
Total equity	\$m	10.8	9.6	12.8	4.5	0.1
CASH FLOW						
		FY22A	FY23A	FY24E	FY25E	FY26E
Net loss for period	\$m	(1.9)	(11.4)	(8.2)	(13.3)	(4.5)
Depreciation & Amortisation	\$m	3.2	1.8	0.5	0.4	0.4
Changes in working capital	\$m	(5.9)	(0.1)	2.2	2.6	0.0
Other	\$m	(11.7)	2.3	0.0	0.0	0.0
Operating cash flow	\$m	(16.3)	(7.3)	(5.6)	(10.3)	(4.1)
Payments for PPE	\$m	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)
Other	\$m	(0.2)	0.0	0.0	0.0	0.0
Investing cash flow	\$m	(0.3)	(0.1)	(0.1)	(0.1)	(0.1)
Equity	\$m	9.1	9.3	10.0	5.0	0.0
Lease liability payments	\$m	(2.4)	(2.2)	(2.2)	(0.3)	(0.3)
Other	\$m	(0.1)	(0.0)	0.0	0.0	0.0
Financing cash flow	\$m	6.6	7.0	7.8	4.7	(0.3)
Cash year end	\$m	8.9	9.2	11.3	5.6	1.0
Free cash flow	\$m	(16.6)	(7.4)	(5.7)	(10.4)	(4.2)

Source: Company reports, MST Access estimates

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# Investment Thesis: Rich Pipeline Potential of Amine Oxidase Inhibitors

## Company profile: focusing on inflammation, fibrosis and cancer

Syntara (known as Pharmaxis until December 2023) is a clinical-stage drug discovery company combining expertise in amine oxidase biochemistry and a proprietary medicinal chemistry platform. The common factor across Syntara's clinical pipeline is a focus on dysfunction affecting the extracellular matrix (ECM), with the company working to develop novel small molecule drugs for diseases stemming from, or involving, inflammation and fibrosis. Fibrosis results from unregulated collagen production and is characterised by overgrowth, hardening, and/or scarring of various tissues, and can affect every organ system, often leading to organ malfunction and high morbidity/mortality<sup>1</sup>.

Syntara's amine oxidase drugs are either 'best-in-class' or 'first-in-class' irreversible<sup>2</sup> small molecule inhibitors of amine oxidase enzymes associated with ECM dysfunction. The company is building its portfolio of drugs with a view to targeting existing unmet needs across a range of inflammatory/fibrotic-related disease areas including:

- **cancers** – stromal (fibrotic) cancers such as pancreatic and liver cancer, myelofibrosis, and other blood cancers
- **organ diseases** – NASH, pulmonary fibrosis, chronic kidney disease, liver fibrosis
- **fibrotic scarring** from burns and other trauma.

## Future growth: drug portfolio to inhibit inflammation/fibrosis, which underpin many conditions

### Overall focus on dysfunction of the ECM, a key element in many diseases with high unmet need

The ECM is a network of fibres, collagen and other proteins that link cells to form tissues; it also provides key signals to cells and regulates the movement of molecules between them. Syntara is working to develop powerful inhibitors of enzymes that affect the ECM, using amine oxidase chemistry and other technologies, in order to develop new medicines for blood cancers and inflammatory and fibrosis-related conditions. Many of these diseases have high unmet need.

### Amine oxidase platform generating multiple candidates, with many more possibilities

Syntara's drug discovery platform focuses on amine oxidases, an important class of regulatory enzymes widespread in the human body whose biological function depends on cofactors and location in human tissue and organs<sup>3</sup>. Syntara's clinical strategy of focusing on targets that have been independently validated in diseases with limited treatment options and where it can use its amine oxidase platform has generated 5 new drug candidates over the last 8 years.

### A rare combination of skills and assets to facilitate bench-to-bedside research

Syntara has brought a combination of assets and skills to its drug discovery platform which underpin the company's powerful capability to harness in-house scientific research to develop clinical trial programs and create novel treatments, a 'bench-to-bedside' process known as 'translational research'. This capability, unusual in an Australian biotech, creates efficiencies in drug discovery, shortens lead optimisation times, and has generated a rich pipeline of product candidates. The pillars of the company's translational research capability include a highly experienced research team; proprietary assays (novel bio probes for measuring enzyme activity); and a deep understanding of the chemistry, biology, and pharmacology of amine oxidases and related clinical translational approaches.

The company's clinical development efforts are primarily focused on developing novel drugs targeting a subset of oxidase enzymes known as lysyl oxidases. This family of enzymes is associated with the development of fibrosis by cross linking collagen and elastin, resulting in hardened, poorly degradable scar-like tissue.

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<sup>1</sup> Shared and distinct mechanisms of fibrosis – Distler et al (2019).

<sup>2</sup> Irreversible inhibitors bind to the enzyme to form an enzyme-inhibitor complex which dissociates slowly or does not dissociate at all. Such inhibitors often form a dead complex where the enzyme becomes useless. Drugs such as penicillin are irreversible inhibitors of the enzyme- transpeptidase in bacteria.

<sup>3</sup> Amine Oxidases in Clinical Research: V.Z,Gorkin (1983).

### **Assets across the clinical pipeline, with four Phase 2 trials**

The recent addition of the Phase 2 clinical trial in myelodysplastic syndrome means that Syntara will have four active Phase 2 trials in its clinical pipeline by the end of CY24. As such, management expects a period of strong newsflow as these trials generate results over the next 18 months. (Syntara's drug candidate names, which previously began with PXS, now all begin with SNT – but have retained the subsequent numbering. Thus, for example, PXS-5505 is now SNT-5505).

# Syntara's Clinical Pipeline: An Overview of the Assets

Syntara has five drug candidates, four of which have reached the Phase 2 clinical trials stage (see Figure 1).

**Figure 1: Syntara's clinical pipeline now with four Phase 2 programs**

Drug	Indication	STAGE				Status
		Discovery	Pre-clinical	Phase 1	Phase 2	
SNT-5505	Myelofibrosis					First patient 4QCY23
SNT-5505	Myelodysplastic syndrome					First patient expected 4QCY24
SNT-5505	Scar prevention - burns					First patient expected 1HCY24
SNT-6302	Scar modification					Planning
SNT-4728	IRBD/Parkinson's Disease					Recruiting
SNT-5382	Organ fibrosis					Clinical safety & target engagement confirmed
SNT-8370	Inflammation					IND-enabling package complete

Source: Syntara.

## SNT-5505 – Syntara's most advanced drug candidate

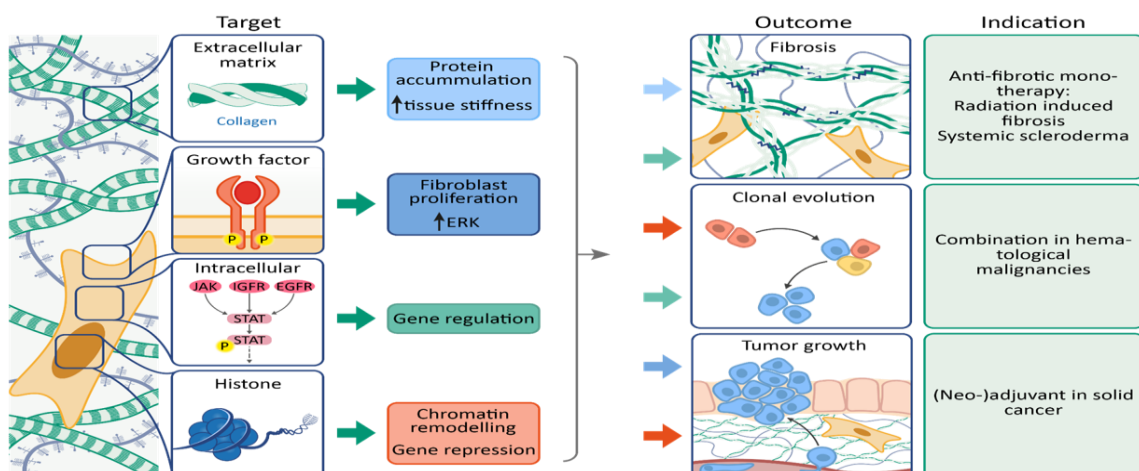
The company's most advanced clinical asset, SNT-5505, targeting primary myelofibrosis (a rare blood cancer characterised by bone marrow fibrosis), is now in Phase 2 clinical trials. SNT-5505 is a novel small molecule and irreversible inhibitor to key enzymes involved in the formation of collagen, specifically the lysyl oxidase (LOX) family of proteins.

The overproduction of LOX proteins (LOXL and LOX1–4) is implicated in many conditions of chronic inflammation and pathological fibrosis. These enzymes start the cross-linking of collagen and elastin. Some disease conditions lead to too much cross-linking, which create hardened fibrotic tissue in organs and around tumours (Figure 2, top left).

Inhibiting LOX proteins also reduces the extent to which growth factors are activated, which also slows fibrosis (Figure 2, middle left), and halt other effects of these proteins (including changing gene expression and promoting clonal selection) which are associated with blood cancers and solid tumours.

SNT-5505 has a novel mechanism of action which fully inhibits all LOX enzymes, thereby preventing the cross-linking of collagen and elastin and the deposition of fibrosis. SNT-5505 is an oral pan-LOX inhibitor and, unlike currently available drug options like JAK inhibitors (ruxolitinib and fedratinib), which provide symptomatic relief, holds promise as a potential disease-modifying treatment. Notably, and despite the limited clinical utility of current treatments, annual sales globally of these drugs are estimated at US\$1bn.

**Figure 2: The effects of inhibiting lysyl oxidases**



Source: Syntara.

## Other focus areas in the pipeline

Syntara is also advancing both oral and topical pan-LOX inhibitors in scar prevention and scar modification programs as part of an ongoing collaboration with Professor Fiona Wood and the University of Western Australia. SNT-4728 is being studied in collaboration with Parkinson's UK as a best-in-class SSAO/MAOB inhibitor to treat sleep disorders and slow progression of neurodegenerative diseases like Parkinson's by reducing neuroinflammation. Other Syntara drug candidates target fibrotic and inflammatory diseases such as kidney fibrosis, NASH, pulmonary fibrosis and cardiac fibrosis.

## SNT-5505 in Blood Cancer: Ongoing Trial Joined by New Trial for Areas of High Unmet Need

### Ongoing trial: myelofibrosis (orphan disease) – continuing investigation into potentially best-in-class oral monotherapy and combination

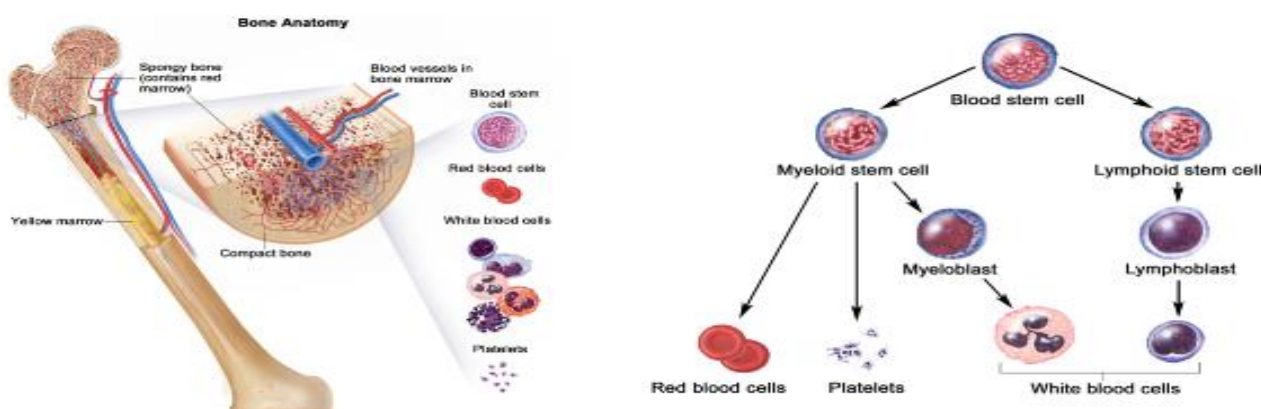
The company's lead asset SNT-5505 is a potentially best-in-class, oral drug inhibitor of all lysyl oxidase family members (LOX, LOXL1, 2, 3 & 4), and as such is referred to as a pan-LOX inhibitor. In pre-clinical models of myelofibrosis (MF), PXS-5505 reversed the bone marrow fibrosis that drives morbidity and mortality in this disease and reduced many of the abnormalities associated with it.

SNT-5505 received IND approval and was granted FDA Orphan Drug Designation in July 2020 for the treatment of primary MF as a monotherapy and progressed to a Phase 1c/2 clinical trial (MF-101) that began recruitment in 1Q2021. This followed the completion of the of a dose escalating safety study in which assessment with Syntara's proprietary assays of the highest dose showed inhibition of the target enzymes, LOX and LOXL2, at greater than 90% over a 24-hour period at days 7 and 28. A review of the result by the trials safety committee deemed SNT-5505 to be well tolerated with no serious treatment-related adverse events.

### Disease overview and market opportunity

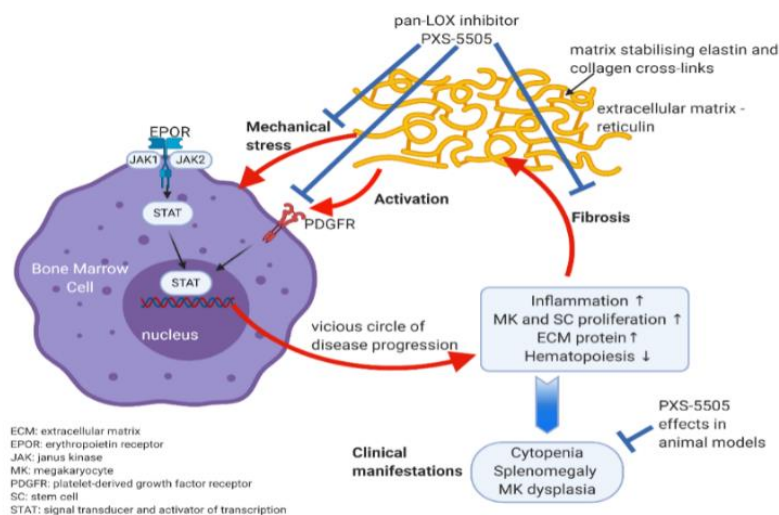
MF is a rare type of bone marrow cancer characterised by a build-up of scar tissue (fibrosis) that disrupts the body's normal production of blood cells. It occurs when bone marrow stem cells develop changes (mutations) in their DNA. MF causes extensive scarring in bone marrow, leading to severe anaemia that can cause weakness and fatigue. Bone marrow scarring can also lead to a low number of blood-clotting cells called platelets, which increases the risk of bleeding. MF often causes an enlarged spleen. The disease affects 0.5–1.5 per 100,000 people worldwide with typical onset between 50 and 80 years of age. A significant number of patients (~11%) transition to leukemia. Once diagnosed, patients have an average life expectancy of ~five years.

**Figure 3: Bone marrow tissue is replaced with fibrotic tissue in MF, which interferes with blood cell product**



Source: [www.cancer.gov](http://www.cancer.gov).

**Figure 4: How SNT-5505 (formerly PXS-5505) works in MF**



Source: Syntara.

## Competitive landscape and current treatments

### Standard therapy and limitations

Allogeneic stem cell transplantation is the only curative treatment for MF currently, involving the transfer by infusion of blood-forming stem cells from a donor to patient essentially replacing defective stem cells. Before the procedure, the patient receives chemotherapy and/or radiation therapy to eradicate diseased bone marrow. A cure rate of 30–65% has been reported with this treatment, but it carries an increased mortality risk.

In 2011, Incyte became the first company on the market with targeted therapy specific to MF, with its JAK inhibitor Jakafi/Jakavi approved in the first-line setting in 2011. Nonetheless, JAK inhibitors only provide symptomatic relief plus some limited survival improvement.

In contrast, SNT-5505 has shown promise of modifying the condition itself, which could support a role in combination therapies for MF. This is now being evaluated in the combination arm of the MF 101 Phase 2 clinical trial.

### Current competitor development pipelines in MF

The most recent approvals for MF have been for JAK inhibitors. In February 2022, the FDA approved pacritinib (Vonjo), a JAK-2 inhibitor, for the treatment of patients with intermediate- or high-risk primary or secondary (post-polycythaemia vera or post-essential thrombocythemia) MF with a platelet count below  $50 \times 10^9/L$ .<sup>1</sup> Additionally, the regulatory agency approved momelotinib (Ojjaara), a JAK1 and JAK2 inhibitor, for the treatment of patients with intermediate- or high-risk MF, including primary MF or secondary MF, and anaemia in September 2023.

Figure 5 highlights a selection of late-stage MF drug candidates currently in development.

**Figure 5: Competitor late-stage development pipelines in MF**

Product	Company	Product type	Comments	Target date	Clinical ID	Phase
Imetelstat	Geron Corp	Telomerase inhibitor	A Study Comparing Imetelstat Versus Best Available Therapy for the Treatment of Intermediate-2 or High-risk MF Who Have Not Responded to JAK-Inhibitor Treatment.	Apr-26	NCT04576156	3
Navitoclax/Ruxolitinib	AbbVie	BCL-2 inhibitor /JAK inhibitor	Study of Oral Navitoclax Tablet in Combination With Oral Ruxolitinib Tablet to Assess Change in Spleen Volume in Adult Participants With Relapsed/Refractory MF	Jan-31	NCT04468984	3
Pacritinib	CTI BioPharma	JAK2 inhibitor	Study of Pacritinib in Patients With Primary MF, Post Polycythemia Vera MF, or Post-Essential Thrombocythemia MF	Dec-25	NCT03165734	3
Parsaclisib/Ruxolitinib	Incyte Corp	PI3Kδ Inhibitor/JAK inhibitor	Evaluate the Efficacy and Safety of Parsaclisib and Ruxolitinib in Participants With MF (LIMBER-313)	Apr-24	NCT04551066	3
KRT-232	Kartos Therapeutics	MDM2 antagonist	KRT-232 Versus Best Available Therapy for the Treatment of Subjects With MF Who Are Relapsed or Refractory to JAK Inhibitor Treatment	Dec-25	NCT03662126	3
CPI-0610	Constellation Pharm.	BET inhibitor	Comparing CPI-0610 and ruxolitinib with placebo and ruxolitinib in MF patients that have not been exposed previously to Janus kinase inhibitors.	Apr-27	NCT04603495	3

Source: [clinicaltrials.gov](https://clinicaltrials.gov).

### Trial update: Phase 2 trial of SNT-5505 + ruxolitinib combination arm

SNT-5505 is in a global Phase 2 study as a monotherapy in MF patients who are intolerant to, unresponsive to or ineligible for treatment with approved JAK inhibitor drugs. Following the approval of a clinical trial protocol amendment by global regulators, including the FDA, Syntara added an additional arm to the trial to evaluate the impact of SNT-5505 when given to patients who are already receiving a stable dose of the standard of care ruxolitinib (JAK inhibitor), for a period of 12 months utilising existing trial sites. The combination arm is being conducted at the same dose currently used in the monotherapy arm.

The first patient in the follow-on study where SNT-5505 is being dosed in combination with the JAK inhibitor ruxolitinib in MF patients was recruited in December 2023. The study is on track to be fully recruited by mid-2024 with the first preliminary data ready for presentation at the December 2024 ASH<sup>4</sup> conference.

<sup>4</sup> The American Society of Hematology (ASH) Conference is the premier event in malignant and non-malignant hematology.

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## New trial: myelodysplastic syndrome (MDS) – investigating a new blood cancer indication

### Disease overview and market opportunity

Myelodysplastic syndrome (MDS) is a group of disorders that gradually affect the ability of a person's bone marrow to produce normal blood cells. As a result, immature blood cells in the bone marrow do not mature or become healthy blood cells, leading to inadequate production of healthy blood cells.

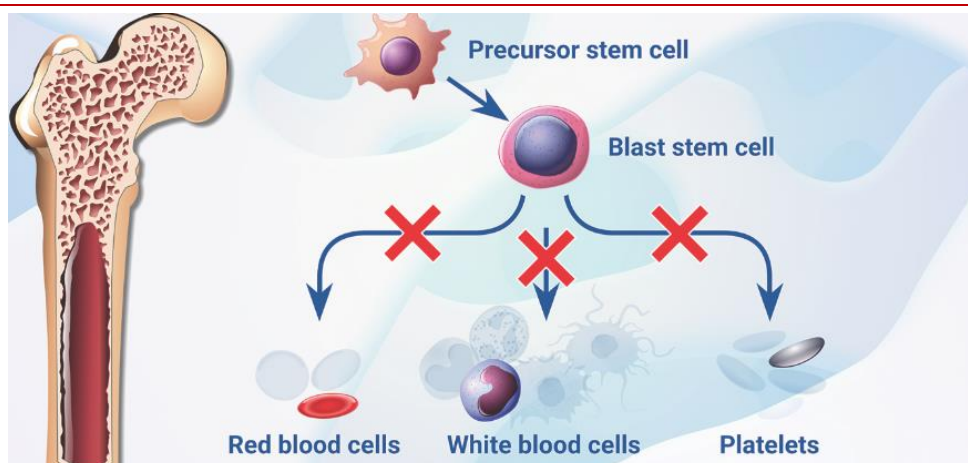
The different types of MDS are diagnosed based on certain changes in the blood cells and bone marrow. Age and past treatment with chemotherapy or radiation therapy affect the risk of MDS.

Tests that examine the blood and bone marrow are used to diagnose MDS. Certain factors affect the disease's prognosis and treatment options. In MDS, abnormal tissue growth can lead to bone marrow failure, often resulting in low blood counts, infections, and dependency on blood transfusions. It also carries an increased risk of progressing to acute myeloid leukemia (AML), a more aggressive form of blood cancer.

People with MDS often show non-specific and variable symptoms. These can include tiredness due to low red blood cells (anaemia), a higher chance of infections because of low white blood cells (neutropenia), and a tendency to bleed easily or bruise due to low platelets (thrombocytopenia) and platelet dysfunction (thrombocytopathy).

The incidence of MDS in the general population is 4.5 cases per 100,000 people per year<sup>5</sup>. It is more common in males than females, with rates of 6.2 and 3.3 per 100,000 people per year, respectively. The incidence increases significantly with age. For individuals under 40 years old, it is around 0.1 per 100,000 people per year, rising to 26.9 in those aged 70–79 and increasing further to 55.4 among those aged 80+. The overall 5-year survival rate for MDS patients once they become dependent on transfusions is only 37%.

**Figure 6: In MDS, blood cells that are formed in the bone marrow never mature fully to become normal blood cells**



Source: Syntara.

### Competitive landscape and current treatments

#### Standard therapy and limitations

High-risk MDS patients are typically treated with intensive chemotherapy – the same treatment that is used to treat AML – which aims to kill a significant proportion of the diseased cells in the bone marrow to allow the bone marrow to work normally again (in other words, to put the patient into remission).

Low-intensity or non-intensive treatment aims to slow the progression of the disease. It may be considered if blood counts are quite low or falling, or if there are not signs that the disease is developing into leukaemia. Low-intensity therapies include HMAs (hypomethylating agents) or biologic response modifiers.

HMAs (azacytidine, intravenous decitabine, and oral decitabine), are approved by the FDA for the treatment of MDS. Azacytidine is the current standard of care and is off patent. For patients with higher-risk MDS, initial responses to HMA therapy are limited (40–50%) and often short-lived. As such, there

<sup>5</sup> Current challenges and unmet medical needs in myelodysplastic syndromes: Platzbecker et al (2021)

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is an urgent unmet need for additional options for patients failing HMA therapy as well as unmet need for patients with MDS after failure of first-line therapy.

### Current treatments on the market

The number of approved drugs for MDS is limited. However, approximately 120+ key companies are developing therapies for MDS. These companies are evaluating agents with different mechanisms of action, but most are still in the early stages of development.

Figure 7 highlights a selection of late-stage MDS drug candidates currently in development.

**Figure 7: Competitor late-stage development pipelines in MDS**

Product	Company	Product type	Comments	Target date	Clinical ID	Phase
Imetelstat	Geron	First-in-class telomerase inhibitor	Study to evaluate Imetelstat in transfusion-dependent subjects with low or intermediate risk MDS	Oct-26	NCT02598661	3
Luspatercept	Celgene	Erythroid maturation agent	Study to compare the efficacy and safety of Luspatercept vs Epoetin Alfa for the treatment of anaemia due to very low, low, or intermediate risk MDS	Sep-27	NCT03682536	3
Venetoclax	AbbVie	B-cell lymphoma-2 (BCL-2) inhibitor	Study of Venetoclax tablet with IV or SC Azacitidine to assess change in disease activity in adults with newly diagnosed higher-risk MDS	Feb-25	NCT04401748	3
Sabatolimab (MBG453)	Novartis	Immunotherapy	Study of efficacy and safety of MBG453 plus Azacitidine in subjects with intermediate, high or very high risk MDS	Jan-27	NCT04266301	3

Source: [clinicaltrials.gov](https://clinicaltrials.gov).

### Trial update: SNT-5505 combination trial

The planned trial of SNT-5505 in MDS is based on a scientific collaboration with the University of Heidelberg, which published work in *Nature Communication* in early 2023 on the role of LOX enzymes in MDS and the effect of combining HMA 5-azacytidine with SNT-5505. The authors found that the significant increase in red blood cell production evidenced in their studies makes a strong case for trialling SNT-5505 combined with 5-azacytidine (the current standard of care in MDS patients), especially for those who are anaemic.

The combination trial will feature a dose escalation phase where up to 9 MDS patients who are transfusion dependent will be treated with a fixed dose of SNT-5505 and two different doses of HMA, followed by a dose-expansion phase where 30 patients will be treated for 6 months on the dose combination selected in the first phase based on tolerability and efficacy.

In this study, there will be a phase where the dose of SNT-5505 remains constant, and nine transfusion-dependent MDS patients will receive treatment with two different doses of an HMA. Following this dose escalation phase, a dose expansion phase will involve treating 30 patients for six months with the selected dose combination from the first phase, determined based on tolerability and effectiveness. The study will assess endpoints such as decreased reliance on transfusions, changes in blood parameters, and improvements in quality of life. The company expects that results from the dose escalation phase, including safety and initial effectiveness measures, will be available around mid-2025.

# Valuation

We value Syntara at A\$234m or A\$0.20 per share, fully diluted, based on sum-of-the-parts (SOTP). We use a risk-adjusted net present value (rNPV) method to value the three lead clinical assets of SNT-5505, SNT-6302 and SNT-4728 through to 2038, consistent with expiry of current patent families, with current shares on issue of 1,191,38,576. There are currently 45,544,420 options (including directors options) outstanding, exercisable at various prices. A breakdown of the SOTP valuation is shown in Figure 8. Our valuation incorporates A\$5.69m in cash at end of December 2023, a 12.5% discount rate, and AUD/USD exchange rate of 0.70.

**Figure 8: Syntara SOTP valuation summary**

Product	Status	Indications	Dose (delivery)	Launch	Peak sales (US\$m)	NPV (US\$m)	Likelihood of approval	rNPV (A\$m)
SNT-5505	Phase 2	Myelofibrosis (MF)	Oral	2029	1,270	226	20%	63
SNT-5505	Phase 2	Myelodysplastic Syndrome (MDS)	Oral	2030	1,441	238	20%	74
SNT-5505	Phase 2	Scar prevention	Oral	TBD				
SNT-6302	Phase 1c	Keloid scarring*	Topical	2028	567	193	15%	51
SNT-4728	Phase 2	Neuro inflammatory/Neurodegenerative	Oral	2028	1,000	149	12%	51
Bronchitol® and Aridol®	Arna Pharma royalty stream	Cystic fibrosis/Asthma diagnostic	Insufflation	On market			100%	3
Net cash (31 December 2023)								6
Total								247
Shares outstanding (m)								1191
Options								46
rNPV/share (A\$) fully diluted								0.20

\* Phase 1c trial will evaluate SNT-6302 as both a prophylactic and treatment in scarring, target indication assumed as treatment for keloid scarring

Source: MST Access.

Our out-licensing assumptions incorporate upfront payments of A\$39m and royalty streams of 11% for each asset, based on the previous out-licencing of PXS-4728A (now SNT-4728). Figure 9 highlights our key valuation assumptions.

**Figure 9: Key valuation assumptions**

Asset/indication	Metrics	Assumptions
<b>SNT-5505</b>		
Myelofibrosis	Target population	Patients with primary, post-polycythemia vera or post-essential thrombocythemia myelofibrosis in the United States and Europe (France, Italy, UK, Germany, Spain).
	Pricing	<b>US\$100,000</b> ; Pricing benchmarked to current SOC (1) Jakafi (Ruxolitinib) average per month cost of US\$7k or US\$84k per year (2) Inrebic (fedratinib) average per month cost of US\$10k or US\$120k per year
	Trial timelines	Assuming launch in 2029
<b>SNT-5505</b>		
Myelodysplastic syndrome	Target population	In the United States, the incidence of MDS in the general population is estimated at 4.5 cases per 100,000. Prevalence set at 60,000.
	Pricing	<b>US\$144,000</b> ; Pricing benchmarked to venetoclax costs estimated at US\$12k per month.
	Trial timelines	Assuming launch in 2030
<b>SNT-6302</b>		
Keloid scars	Target population	Based on keloid scar prevalence of c. 300k patients in the United States and c. 460k in Europe.
	Pricing	<b>US\$4,000</b> ; Pricing benchmarked to laser therapy and set at US\$1,000 per 3 month course of treatment. Expecting 4 rounds of treatment (4 x 3mth course). Keloid scarring more difficult to treat.
	Trial timelines	Assuming launch in 2028
<b>SNT-4728</b>		
IRBD and Parkinson's disease	Target population	In the United States, addressable market of 12% of population or ~400,000 patients. In Europe (France, Italy, UK, Germany, Spain) addressable market of around 13% of population or ~665,000 patients.
	Pricing	<b>US\$5,000</b> ; No comparator but general assumption for treating chronic disease such as Parkinson's disease.
	Trial timelines	Assuming launch in 2028

Source: MST Access.

Notwithstanding the expected newsflow generated by 4 Phase 2 trials over the next 18 months, we think the advanced stage and potential for positive efficacy data in MF alone could attract a strategic partner or acquirer. Figure 10 highlights recent transactions and the potential commercial opportunity in MF.

**Figure 10: Comparator transactions in myelofibrosis**

Date	Target/Acquirer	Drug Name	Lead Indication / Phase (at transaction)	Deal Type	Upfront / Milestones (USD)	Earnout Payments / Royalty Rate (%)
Jan-18	Celgene/Impact Biomedicines	Fedratinib	Myelofibrosis & Polycythemia vera (Successful Phase 3 Trials)	Acquisition	\$1.1b/\$1.25b	None
Sep-20	Forbuis/Bristol Myers Squibb	AVID200	Myelofibrosis (Phase 1)	Acquisition	undisclosed	undisclosed
Nov-22	Imago Biosciences /Merck	Bomedemstat	Haematology (Phase 2)	Acquisition	\$1.35b	None
Dec-20	Cellenkos/Incyte	Combination of Ruxolitinib & CK0804	Myelofibrosis (Phase 1b)	Licensing	If option exercised US\$20m Licensing fee Sales Milestone up to US\$294.5m	Tiered royalties:Mid single to low double digits
Jul-22	Sierra Oncology/GSK	Momelotinib	Myelofibrosis (FDA Filed –June)	Acquisition	\$1.9b	None
Jun-23	CTI BioPharma Corp/Swedish Orphan Biovitrum AB	Pacritinib	Myelofibrosis (Primary/Secondary - approved)	Acquisition	\$1.7b	None

Source: Syntara.

# Risks

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

In addition, key stock-specific sensitivities are detailed below.

## Clinical risk

The company's medicinal chemistry expertise and proprietary assays underpin substantial drug discovery capabilities and provide significant opportunities to design, test, and optimise potential drug candidates in preclinical settings. This has been demonstrated by the development of a broad portfolio of small molecule amine oxidase inhibitors over the last five years.

However, drug development carries a raft of associated clinical risks including clinical trial delays or failures which could have a significant impact on the progress of individual assets and related candidates in the pipeline. The most important near-term development sensitivity is related to SNT-5505, given its Orphan Drug Designation status, and to a lesser extent SNT-6302. Both assets are pan-LOX inhibitors and are entering Phase 2a and Phase 1c trials respectively designed to demonstrate efficacy in patients. Clinical asset-specific risk considerations also include:

- **Clinical target risk:** Although SNT-5505 was shown to be well tolerated at the highest dose given and has delivered complete inhibition of the target enzymes, Phase 2a will answer the question of whether the disease-modifying effect seen in animal models can be replicated in patients.
- **Clinical development path risk:** Targeting of keloid scarring using SNT-6302 could face additional challenges from a clinical development perspective given the heterogeneity of these scars, variability in patient and skin types, and the less objective measures available to monitor progress.

As such, success at this stage will determine the next leg of development activities and have a major bearing on partnering and commercialisation prospects for both clinical assets.

## Key person risk

This is also a consideration for Syntara, given its reliance on its drug discovery engine and the highly experienced team currently in place.

## Regulatory risk

Market approval will depend on satisfying the requirements of multiple regulators. As in the case of Bronchitol®, this can result in additional data requirements and lead to time delays and increased funding needs. However, the company's experience in bringing Bronchitol® to market despite such delays bodes well for future submissions.

## Funding risk

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

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