EVOLUTION CAPITAL

ASX:SNT
Healthcare
Initiation Report

Thursday, 27 March 2025

Pioneering LOX Inhibitors in Haematological Cancers

Evolution initiates coverage on Syntara Limited ("Syntara" or "SNT") with a fair valuation of A$0.235 per share, representing approximately 218% expected upside from the last closing share price of A$0.074. Syntara is developing first-in-class and best-in-class LOX-inhibitors for the treatment of diseases characterised by fibrosis of the extracellular matrix – the structural backbone of the cells and tissues in our body.

Breakthrough MF Treatment with Promising Clinical Data: Interim results from the ongoing phase 2 clinical trial of SNT-5505 in Myelofibrosis (MF) show impressive efficacy with 80% of patients achieving at least 50% reduction in TSS (Total Symptom Score) by week 38, as well as sustained spleen volume reductions. Unlike JAK inhibitors – today's best-in-class therapeutical line – that only manage symptoms, SNT-5505 directly targets fibrosis – the underlying cause of myelofibrosis, indicating the potential to be a disease-modifying treatment. Phase 2 success to date lays the perfect foundation for a pivotal phase 3 trial expected to commence late 2025 or early 2026.

Significant Market Opportunity: Syntara's pipeline targets substantial markets including myelofibrosis (US$2.5B), myelodysplastic syndrome (US$2.88B), skin scarring (US$26.5B), and Parkinson's disease (US$6.59B). The MF and MDS space has seen lucrative M&A activity, with big pharma eagerly acquiring drug developers showing disease-modifying potential at similar development stages to Syntara. Recent examples include GSK's acquisition of Sierra Oncology for US$1.9 billion and Merck's acquisition of Acceleron Pharma for US$11.5 billion. Similarly, licensing deals include Takeda's agreement with Keros Therapeutics (US$200M upfront, up to US$1.1B in milestones), and Incyte's deal with Novartis for ruxolitinib (US$150M upfront, up to US$1.1B in milestones). These precedents highlight the tremendous value potential for Syntara if SNT-5505 continues to demonstrate clinical success.

In-House Drug Discovery Capability: Unlike many ASX-listed biotech peers reliant on outsourced research, Syntara operates its own laboratory, enabling rapid iteration and cost-efficient development. With a lean team of under 20 staff, they've generated outsized value through five recently launched clinical trials, demonstrating exceptional operational efficiency. The recent announcement of SNT-9465 epitomizes this efficiency.

Share Price	$0.074
Fair Valuation	$0.235
Recommendation	SPEC BUY
Upside	218%
52-Week Range	$0.014 - $0.095
Market Cap	~$123.2M
Cash	$18.1M
Enterprise Value	$105.1M
Free Float	~85%

Price Performance

Company Overview

Syntara Limited (ASX:SNT) is a clinical-stage drug developer with in-house drug discovery expertise, focused on innovative treatments for blood cancers, inflammation, and fibrosis. Its lead candidate, SNT-5505, a pan-LOX inhibitor, is showing promising results in myelofibrosis trials. The company is also advancing therapies for myelodysplastic syndrome, neuroinflammation, and skin scarring in collaboration with leading institutions. Listed on the ASX, Syntara is pioneering novel solutions for high unmet medical needs.

Analyst

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Catalyst	Timeline
Initiation of Phase 1c/2 trial for SNT-5505 in low/intermediate-risk MDS	H1 2025
Initiation of Phase 1c/2 trial for SNT-5505 in high-risk MDS (AZALOX expansion phase)	H1 2025
FDA feedback request for next stage of SNT-5505 clinical development in MF	Q2 2025
Additional interim data for Phase 2a trial of SNT-5505 in MF	Q2 2025
Final Phase 2a data for SNT-5505 in MF	H2 2025
Phase 1c data for SNT-5505 in Myelodysplastic Syndrome (MDS)	H2 2025
Phase 2 trial results for SNT-4728 in Parkinson's Disease	H2 2025
Initiation of clinical trials for SNT-6302 in keloid scars & SNT-9465 in hypertrophic scars	H1 2025
Data from Phase 1a/b trial of SNT-9465	H1 2026

Contents

1. Investment Case

Syntara's value proposition is driven by its innovative pipeline of therapeutics targeting high-unmet-need indications, a strategic focus on diseases with significant total addressable markets (TAMs), and in-house drug discovery capabilities. With a portfolio spanning myelofibrosis (MF), myelodysplastic syndromes (MDS), skin scarring, and Parkinson's disease (PD), Syntara is poised to address substantial global healthcare challenges, leveraging its expertise in amine oxidase chemistry to deliver first-in-class and best-in-class solutions.

The Pipeline

The company's lead asset, SNT-5505, a pan-LOX inhibitor, targets MF – a rare bone marrow cancer with a current TAM of US$2.5 billion – offering a transformative approach by addressing the underlying fibrosis that existing therapies like ruxolitinib fail to tackle. Interim Phase 2 data, presented at the 2024 ASH conference in December, showcased its potential, with 80% of patients achieving a ≥50% reduction in Total Symptom Score (TSS50) by week 38 and sustained spleen volume reductions, alongside a pristine safety profile. These are key differentiators that signal its readiness for Phase 3 trials and position it as a potential game-changer in a market hungry for disease-modifying therapies.

Beyond MF, SNT-5505's expansion into MDS, with a TAM of US$2.88 billion in 2023 (projected to exceed US$6.64 billion by 2030), underscores Syntara's ability to increase the commercial potential of its assets across related haematological malignancies. Two upcoming Phase 1c/2 trials in 2025, supported by grants including A$2.5 million from Deutsche Krebshilfe for the AZALOX study, highlight both scientific validation and financial backing, reducing risk and enhancing the likelihood of success in clinical development. Meanwhile, SNT-6302, a topical pan-LOX inhibitor for skin scarring, taps into a massive US$26.5 billion market (2023), projected to reach US$76.2 billion by 2034. The SOLARIA2 trial demonstrated its ability to remodel mature scars – reducing collagen by 30% and enhancing vascularisation – offering a novel alternative to the dominant topical agents like silicone gels, which merely manage symptoms. This positions SNT-6302 as a strong candidate to gain significant share of the lucrative topical treatment segment (65.5% of the market), with plans for trials in scar prevention further amplifying its commercial runway.

Rounding out the pipeline, SNT-4728 targets Parkinson's disease via iRBD, a US$6.59 billion market in 2024. Phase 2 results are expected in H2 2025. Its dual SSAO/MAO-B inhibition addresses neuroinflammation – a root cause overlooked by dopamine-centric therapies – potentially carving out a niche in a field desperate for disease-modifying options.

Clinical Development Advantage

Syntara's prospects for success in further clinical development, regulatory approval, and commercialization are bolstered by its robust track record and operational strengths. The promising Phase 2 MF interim data provides a solid foundation for navigating Phase 3 trials and regulatory discussions. Unlike many ASX-listed biotech peers reliant on outsourced research, Syntara operates its own laboratory in Sydney's North Shore, enabling rapid iteration and cost-efficient development – a key advantage that enhances its agility. This in-house capability, combined with a lean team of under 20 staff generating outsized value through five recently launched clinical trials, underscores Syntara's efficiency. The company's strategic evolution from a broad research entity to a focused biotech with validated assets further strengthens its position, as does its ability to secure partnerships with global leaders like Parkinson's UK and attract interest from potential pharmaceutical collaborators for SNT-5505.

Rounding It Out

Syntara differentiates itself from competitors through its unique mechanistic approach – targeting extracellular matrix dysfunction and fibrosis – where others focus on symptomatic relief or narrower pathways. This is a critical edge in crowded markets like MF, where JAK inhibitors dominate but leave 75% of patients without long-term solutions, or MDS, where hypomethylating agents offer transient benefits. The company's ability to secure government grants and regulatory incentives, such as the seven-year market exclusivity tied to Orphan Drug status, enhances its commercial viability and attractiveness to investors seeking de-risked opportunities. Its seasoned leadership, including CEO Gary Phillips with over 30 years in biotech, further instils confidence in its ability to execute on Phase 3 trials, secure approvals, and drive partnerships or acquisitions. For investors, Syntara represents a rare blend of scientific innovation, market opportunity, and operational excellence, poised to deliver significant returns as it transitions from clinical promise to commercial reality.

SNT Pipeline

Asset	Indication	Stage	Next Milestone	Curren Commercial Opportunity (TAM)
SNT-5505	MF	Phase 2a (Ongoing)	Final data in H2 2025, FDA discussions for Phase 3	US$2.5 billion (2024)[1]
SNT-5505	MDS	Phase 1c/2 (Upcoming)	Phase 1c data in H2 2025	US$2.88 billion (2023)[2]
SNT-5505	MDS	Phase 1b/2 (Upcoming)	Trial to begin Q1 2025 in Germany	
SNT-6302	Skin Scarring	Phase 1c completed (SOLARIA2)	Clinical development planning for scar prevention	US$26.5 billion (2023)[3]
SNT-4728	Parkinson's Disease (iRBD)	Phase 2 (Ongoing)	Trial results expected in H2 2025	US$6.59 billion (2024)[4]

Table 1: Table outlining Syntara's pipeline of assets, their stage of development, and the total addressable market for each indication.

1. *Imarc Group: Myelofibrosis Treatment Market Report by Drug Type (Hydroxyurea, Immunomodulators, JAK Inhibitor, and Others), Treatment Type (Blood Transfusion, Chemotherapy, Androgen Therapy, Stem Cell/Bone Marrow Transplantation, and Others), End User (Hospitals and Clinics, Bone Marrow Transplant Centres, and Others), and Region 2025-2033*
2. *Grand View Research: Myelodysplastic Syndrome Drugs Market Size, Share & Trends Analysis Report By Treatment (Chemotherapy, Immune Treatments), By Route Of Administration, By End-use (Hospitals, Clinics), By Region, And Segment Forecasts, 2024 - 2030*
3. *Precedence research: Scar Treatment Market Size, Share and Trends 2024 to 2034*
4. *Precedence research: Parkinson's Disease Therapeutics Market Size, Share, and Trends 2024 to 2034*

2. SNT-5505: A Breakthrough in Myelofibrosis Treatment

Syntara is at the forefront of drug development for diseases with high unmet medical need, leveraging its expertise in amine oxidase chemistry to create innovative therapies. Among its pipeline, SNT-5505 stands as a beacon of hope for patients with myelofibrosis (MF), a rare and debilitating bone marrow cancer that disrupts normal blood cell production. While existing JAK inhibitors, such as ruxolitinib (RUX), offer symptom relief, they fail to address the underlying fibrosis and disease progression. This is where SNT-5505, a first-in-class pan-LOX inhibitor, introduces a game-changing therapeutic approach.

Myelofibrosis

Myelofibrosis (MF) is a rare but devastating bone marrow cancer that severely disrupts normal blood cell production. It is classified as a myeloproliferative

Myelofibrosis (MF) causes severe anaemia and other debilitating symptoms. Over time, MF often progresses to AML – a cancer of the body's blood forming tissues.

neoplasm (MPN)[1] and is characterised by progressive bone marrow fibrosis[2], leading to severe anaemia, splenomegaly (enlarged spleen), and debilitating constitutional symptoms such as fatigue, night sweats, bone pain, and weight loss. Over time, the disease often progresses to acute leukaemia (a cancer of the body's blood-forming tissues, including the bone marrow and the lymphatic system), significantly worsening prognosis.

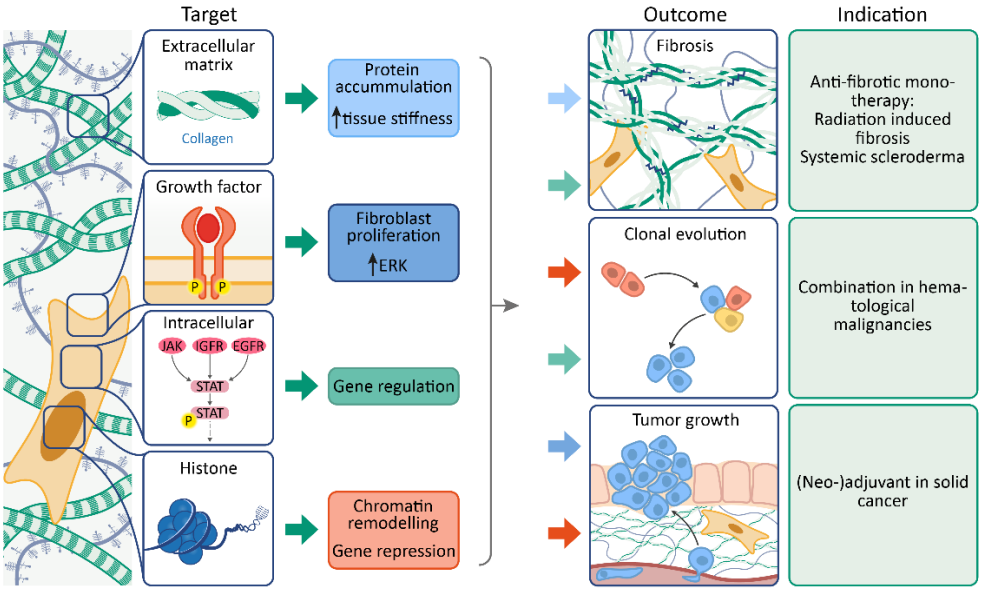

Figure 1: image sourced from Syntara website outlining the target therapeutic areas for their LOX-inhibitor

Epidemiology & Disease Impact

US prevalence of MF is estimated to exceed 30,000 people by 2034. Global prevalence is estimated at a total of 100,000 people today, though this may be an underestimate due to challenges in diagnosis.

While classified as a rare disease, MF has a growing prevalence, particularly among ageing populations. In Australia, approximately 300 to 400 new cases are diagnosed annually. In the United States, the total number of people living with MF is currently estimated at 19,000 to 25,000 and is expected to increase to over 30,000 by 2034. This rise is driven by an ageing population, improved diagnosis, and longer patient survival due to advancing treatments.

Globally, MF affects an estimated 65,000 people across major pharmaceutical markets, including the U.S., Europe, and Japan, with projections indicating that this number will surpass 70,000 by 2034. The disease is estimated to affect approximately 15 per 1 million people worldwide, but the actual burden may be underestimated due to underdiagnosis. As the prevalence of MF continues to rise, the need for innovative treatments targeting the disease's underlying pathology becomes increasingly critical.

Median overall survival for high-risk MF patients is only 2.8 years.

One of the greatest challenges with myelofibrosis is its progressive nature. A 2022 study published in 'blood advances' reported that the median overall survival for high-risk patients is 2.8 years, and that outcomes significantly deteriorate once the disease transforms into acute myeloid leukaemia (AML)[3], which happens in approximately 11% of cases. When myelofibrosis progresses to AML, the prognosis is generally poor. Studies have reported median survival times ranging from approximately 2.6 to 7 months following transformation. Allogeneic stem cell transplantation (allo-SCT) is currently the most effective treatment option for AML secondary to myeloproliferative neoplasms, including myelofibrosis. However,

[1] Myeloproliferative neoplasm (MPN): group of rare blood cancer characterized by the bone marrow producing too many blood cells
[2] Fibrosis: the development of excessive connective tissue in response to injury or disease. In bone marrow fibrosis, the bone marrow is replaced by fibrous scar tissue, hindering blood cell production.
[3] Acute Myeloid Leukaemia: cancer of the blood and bone marrow where the bone marrow produces too many abnormal blood cells, particularly immature white blood cells called blasts.

outcomes remain suboptimal. In a study analysing patients who underwent allo-SCT, the median overall survival post-transplant was 15.3 months.

Additionally, many patients require chronic blood transfusions due to severe anaemia[4], which not only impacts their quality of life but also places a significant burden on healthcare resources.

Current Treatment Options

The current standard of care for MF primarily revolves around Janus kinase (JAK) inhibitors, such as ruxolitinib (RUX). These targeted therapies have transformed the treatment landscape by offering symptomatic relief and reducing spleen volume in patients with MF. However, they do not halt disease progression, and their effectiveness is limited over time.

Ruxolitinib is the current best-in-class treatment for MF. It is a JAK-inhibitor that mitigates inflammation. It was approved in 2011 and has demonstrated reasonable efficacy in reducing spleen volume and easing symptoms.

JAK inhibitors work by blocking the activity of Janus kinases, which are intracellular enzymes that play a critical role in signal transduction for various cytokines[5] and growth factors. The JAK-STAT (Signal Transducer and Activator of Transcription) pathway is essential for normal immune and haematopoietic[6] cell function, but in MF, it is often dysregulated due to mutations in the JAK2, CALR, or MPL genes. These mutations lead to uncontrolled activation of the pathway, resulting in excessive inflammation, bone marrow fibrosis, and the overproduction of abnormal blood cells.

JAK inhibitors, such as ruxolitinib, target JAK1 and JAK2 to mitigate inflammation and manage symptoms like anaemia, night sweats, fatigue, and spleen enlargement. However, they do not reverse fibrosis or alter the disease trajectory fundamentally.

75% of patients discontinue JAK inhibitors within 5 years due to diminishing efficacy, disease progression, or adverse effects. There is an unmet need for a treatment with long-lasting efficacy and safety.

The approval of ruxolitinib by the U.S. Food and Drug Administration (FDA) in 2011 marked a breakthrough in MF management, demonstrating significant benefits in symptom control and spleen volume reduction. Subsequent JAK inhibitors, including fedratinib, pacritinib, and momelotinib, were developed to address ruxolitinib's limitations, such as haematologic toxicity or inadequate response. Yet, despite these options, 75% of patients discontinue JAK inhibitors within five years due to diminishing efficacy, disease progression, or adverse effects, with a median survival of only 14 to 16 months post-discontinuation, underscoring the urgent need for disease-modifying therapies.

When patients discontinue JAK inhibitors due to intolerance, resistance, or disease progression, treatment options become increasingly constrained, leading to a poorer prognosis. The subsequent line of therapy depends on the patient's clinical status and previous treatments. In cases of ruxolitinib failure, switching to another JAK inhibitor, such as fedratinib or pacritinib, may be considered, particularly when specific toxicities like Thrombocytopaenia are involved. Fedratinib, FDA-approved in 2019, has demonstrated efficacy in patients resistant to ruxolitinib but requires careful monitoring due to risks such as encephalopathy. Pacritinib, approved in 2022, offers a viable option for those with severe Thrombocytopaenia, providing both spleen volume reduction and symptom relief in this challenging patient population.

Beyond JAK inhibitors, other treatment options play a vital role in managing MF, particularly for patients who do not respond to or cannot tolerate these therapies. Chemotherapy[7], such as hydroxyurea, is frequently used, especially in patients with significant splenomegaly or elevated white blood cell counts. Hydroxyurea works by reducing the proliferation of abnormal haematopoietic cells, thereby alleviating

[4] Anaemia: a condition where the blood doesn't have enough healthy red blood cells (RBCs) or haemoglobin (oxygen carrying component of RBCs, leading to reduced oxygen delivery to the body's tissues.
[5] Cytokines: proteins that act as chemical messengers to communicate between immune cells. They can stimulate or slow the immune system and are involved in many physiological processes.
[6] Haematopoietic: refers to the process of blood cell formation.
[7] Chemotherapy: the treatment of disease using chemical substances, especially the treatment of cancer by cytotoxic and other drugs.

Chemotherapy is a line of therapy often used where JAK inhibitors fail. It is however quite toxic and shows little to no disease-modification.

symptoms like spleen enlargement and constitutional symptoms. However, it does not address the underlying bone marrow fibrosis or genetic drivers of the disease. Other chemotherapeutic agents, such as cladribine or melphalan, may be employed in specific cases, particularly when rapid cytoreduction[8] is needed, but their use is limited by toxicity and lack of disease-modifying potential.

For patients with severe anaemia – a common and debilitating feature of MF – supportive care options like erythropoiesis-stimulating agents (ESAs), such as erythropoietin or darbepoetin, are often considered. These agents stimulate red blood cell production and may reduce transfusion dependence in select patients with low erythropoietin levels. However, their efficacy is limited in MF due to the underlying bone marrow dysfunction, and they are typically reserved for patients with milder disease. Androgen therapies, such as danazol, represent another supportive option for anaemia management, showing modest success in improving haemoglobin levels in some patients (enhancing oxygen delivery to tissues) though responses are inconsistent and often temporary.

HSCT is the only curative treatment for MF but is highly risky and extremely costly to the patient, with procedures ranging from US$350k to US$800k or more. It is only appropriate for a very small subset of MF patients.

In cases where MF progresses to an accelerated or blast phase (resembling acute leukemia), more aggressive treatments like hypomethylating agents[9] (e.g., azacitidine or decitabine) may be employed. These agents aim to reduce the clonal burden of abnormal cells and delay leukemic transformation, offering a bridge to potentially curative options like allogeneic haematopoietic stem cell transplantation (HSCT). HSCT remains the only known curative treatment for MF, but it is suitable for only a small subset of patients – typically younger individuals with good performance status – due to its high risk of morbidity and mortality. The decision to pursue HSCT often depends on disease risk stratification (e.g., using the Dynamic International Prognostic Scoring System, DIPSS) and the availability of a suitable donor. The cost of HSCT can vary significantly depending on factors such as the country, healthcare system, and individual patient needs. In countries like the United States, the total cost of an HSCT procedure can range from US$350,000 to US$800,000 or more.

Combination therapies involving JAK inhibitors are increasingly being explored to enhance efficacy and address their limitations. For instance, ruxolitinib is sometimes combined with hydroxyurea or ESAs to manage cytopenias while maintaining symptom control. Clinical trials have also investigated pairing JAK inhibitors with hypomethylating agents or immunomodulatory drugs like lenalidomide to target both the inflammatory and proliferative aspects of MF. These combinations aim to improve response rates and durability, though evidence of survival benefit remains limited, and toxicity profiles can complicate their use.

The Economic & Healthcare Burden

Ruxolitinib has an annual cost ranging between US$100k – US$150k per patient. Other JAK inhibitors are priced similarly.

The primary costs associated with MF treatment are immense. Ruxolitinib has an annual cost ranging between US$100,000–$150,000 per patient, depending on dosage and healthcare system pricing. The costs of other JAK inhibitors, such as fedratinib (Inrebic®), pacritinib (Vonjo®), and momelotinib (Ojjaara®), are similarly high, contributing to the overall economic impact of the disease.

Moreover, many patients eventually develop resistance or intolerance to JAK inhibitors, requiring combination therapies, clinical trials, or alternative off-label treatments, further increasing healthcare expenditure. Beyond JAK inhibitors, supportive care measures play a crucial role in managing MF symptoms and complications, adding further financial strain:

[8] Cytoreduction: cancer reduction.
[9] Hypomethylating agents: a class of drugs that inhibit DNA methylation, a key mechanism in the development and progression of certain types of blood cancers.

Supportive care is similarly expensive. Blood transfusions to manage associated anaemia costs typically US$2-3k per session, for example.

- Frequent blood transfusions to manage anaemia (costing approximately US$2,000–$3,000 per session),
- Growth factors such as erythropoiesis-stimulating agents (ESAs) to support red blood cell production (US$5,000–$10,000 annually),
- Iron chelation therapy for transfusion-dependent patients (US$20,000–$40,000 per year),
- Management of splenomegaly, which may require splenectomy ($30,000–$50,000 per procedure) or radiation therapy ($5,000–$20,000 per cycle),
- Hospitalisation costs for severe disease complications, infections, or thrombotic events, which significantly raise annual healthcare costs.
- Additionally, bone marrow transplantation (the only curative option for MF) is a high-risk, high-cost procedure, typically exceeding US$300,000 in upfront costs, with lifelong post-transplant medication adding further expenses.

The cumulative costs of MF treatment, hospitalisations, and long-term management exceed US$1 billion annually in global healthcare expenditures. In the United States alone, the total lifetime cost of treating MF has been estimated to exceed US$500,000 per patient, depending on disease severity. This places an increasing burden on US Medicare, private insurance systems, and out-of-pocket expenses for patients.

In countries with 'universal' healthcare, such as Australia and parts of Europe, MF-related treatments place additional pressure on government-funded programs, requiring subsidisation through reimbursement schemes like Australia's Pharmaceutical Benefits Scheme (PBS) or the UK's National Health Service (NHS). The high cost of JAK inhibitors and ongoing supportive care makes long-term affordability and access to innovative therapies a major policy challenge.

The PBS subsidises ruxolitinib. Under the co-payment structure, general patients pay up to A$31.50 per prescription. For a patient on 5mg twice a day, 6-7 prescriptions are required per annum. For higher-dosing patients, around 13 prescriptions are required per year.

As of February 2025, the Pharmaceutical Benefits Scheme (PBS) in Australia subsidises specific treatments for MF, with ruxolitinib (Jakavi®) being the primary medication available under the scheme. It is indicated for patients with high-risk and Intermediate-2 risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis. It is also available to patients with Intermediate-1 risk MF, provided they exhibit severe disease-related symptoms that are resistant, refractory, or intolerant to available therapies.

To qualify for PBS subsidy, patients must:

- Provide a bone marrow biopsy report confirming the diagnosis.
- Present a risk classification according to the International Prognostic Scoring System (IPSS), Dynamic International Prognostic Scoring System (DIPSS), or Age-Adjusted DIPSS.
- For Intermediate-1 risk patients, demonstrate severe symptoms unresponsive to existing treatments.

Another emerging treatment option for myelofibrosis is momelotinib (Omjjara®), a JAK inhibitor that has demonstrated efficacy in treating patients with moderate to severe anaemia, a common complication of the disease. Unlike ruxolitinib, momelotinib offers the additional benefit of reducing the need for blood transfusions by addressing anaemia alongside myelofibrosis symptoms. In November 2024, the Pharmaceutical Benefits Advisory Committee (PBAC) recommended its inclusion on the PBS for treating myelofibrosis patients with

moderate to severe anaemia. However, as of January 2025, the listing process is still underway, with government approvals yet to be finalised.

The Science Behind SNT-5505

Lysyl Oxidases are a family of enzymes that play a crucial role in the stabilisation and remodelling of the ECM.

Current MF treatments primarily reduce symptoms or slow disease progression, but they rarely address the disease's root cause: excessive fibrosis in the bone marrow. At the heart of SNT-5505's innovation is its unique ability to target and clear this fibrosis. By inhibiting lysyl oxidases (LOX), enzymes that crosslink structural proteins in the ECM and stiffen tissues, SNT-5505 disrupts the fibrotic network that fosters abnormal stem cell development. Rather than merely dampening inflammation, SNT-5505 aims to remodel the bone marrow microenvironment, potentially enabling the production of healthier blood cells, therefore achieving deeper, more durable disease modification.

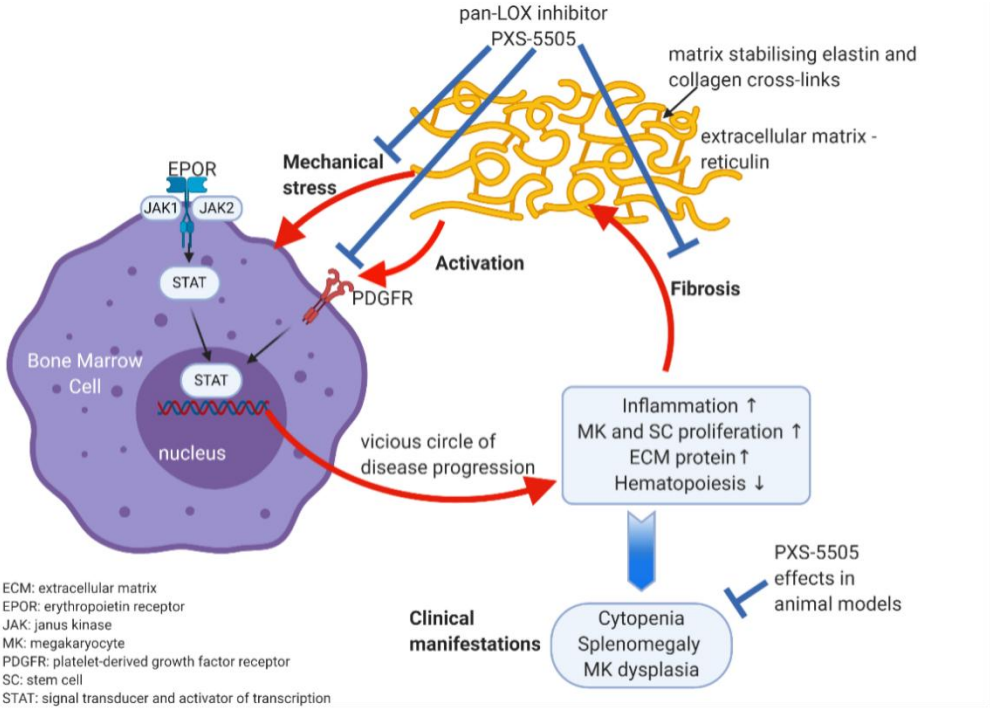

Figure 2: diagram sourced from Syntara website. It outline how SNT-5505 works in myelofibrosis.

LOX Inhibitors: What are they?

Excessive LOX activity contributes to fibrosis. Inhibition of LOX can reverse tissue stiffening, an underlying characteristic of MF.

LOX inhibitors represent an innovative class of therapeutics targeting extracellular matrix (ECM)[10] remodelling, with promising applications in cancer and fibrosis. The LOX enzyme family plays a fundamental role in crosslinking collagen[11] and elastin, ensuring tissue integrity through the shaping of ECM. While essential for normal wound healing and maintenance, excessive LOX activity contributes to pathological conditions such as cancer progression, and fibrosis. By inhibiting LOX, these drugs aim to prevent or reverse the tissue stiffening that underlies these diseases.

LOX inhibitors work by suppressing the enzymatic activity responsible for excessive ECM crosslinking. This prevents abnormal tissue rigidity, which drives fibrosis and disease progression. In cancer, LOX remodels the tumour microenvironment, promoting metastasis by increasing stiffness and enhancing invasiveness. Inhibiting LOX disrupts these processes, potentially limiting tumour spread and improving responsiveness to conventional therapies. Similarly, in fibrotic diseases, blocking LOX

[10] Extracellular Matrix (ECM): a large network of proteins and other molecules that surround, support, and give structure to cells and tissues in the body.
[11] Collagen: the main structural protein in the ECM. Elastin is also a component of ECM.

activity mitigates pathological connective tissue accumulation, helping preserve organ function.

The History

The development of LOX inhibitors has evolved significantly over the past decades. Early research in the 1990s and 2000s established the role of LOX in fibrosis and cancer, paving the way for therapeutic interventions. Initial LOX inhibitors, such as beta-aminopropionitrile (BAPN), demonstrated promising anti-fibrotic effects but suffered from significant off-target effects and associated toxicity, limiting their clinical utility. More recent advancements in medicinal chemistry have led to the creation of selective and potent LOX inhibitors with improved safety profiles. These second-generation inhibitors have demonstrated efficacy in preclinical and early clinical studies, providing hope for their application in a variety of diseases.

No LOX inhibitors have yet been approved for widespread clinical use.

Historically, LOX inhibitors have been explored for a range of indications. In oncology, LOX inhibition has been investigated as a strategy to enhance the effectiveness of chemotherapy and immunotherapy by altering the tumour microenvironment. In fibrotic diseases, LOX inhibitors have shown promise in reducing fibrosis in conditions such as pulmonary fibrosis, liver cirrhosis, and skin scarring. Additionally, in neurodegenerative diseases, LOX inhibitors have been studied for their potential to reduce neuroinflammation and oxidative damage, thereby slowing disease progression. Despite this broad interest, the clinical translation of LOX inhibitors has been challenging, with many compounds failing to progress beyond early-stage trials. No LOX inhibitors have yet been approved for widespread clinical use, but several are in advanced development.

SNT-5505 in Action: Clinical Development Progress

Phase 1 Monotherapy Trial (2021) – Dose Escalation

The initial Phase 1 trial, conducted in 2021, was a dose-escalation study to assess safety, tolerability, and pharmacokinetics in myelofibrosis patients. This phase involved testing three different dosage levels, with the highest dose showing over 90% inhibition of target enzymes LOX and LOXL2. The trial demonstrated good tolerability, with no serious treatment-related adverse events, laying a strong foundation for advancing to efficacy evaluation. This phase was crucial for establishing a safe and effective dose, with the safety committee approving progression to a six-month Phase 2 study, highlighting the drug's potential as a well-tolerated treatment option.

Phase 2a Monotherapy Trial (2021–2023) – Expansion

The phase 2a monotherapy arm showed positive results with no SAEs, improvement in fibrosis, and improvement in haemoglobin levels.

Following the Phase 1 results, the trial expanded into a Phase 2a monotherapy study, focusing on efficacy in patients who were intolerant, unresponsive, or ineligible for JAK inhibitors like ruxolitinib. This open-label study, conducted from 2021 to 2023, involved 24 patients treated at the selected dose of 200 mg twice daily for at least six months. Interim data from 10 patients, reported in July 2023, showed promising results: the drug was well-tolerated with no serious treatment-related adverse events, 60% of patients exhibited a one-grade improvement in fibrosis (e.g., from MF-3 to MF-2 on the WHO scale), 70% had stable or improved haemoglobin levels, and 80% had stable or improved platelet counts over 24 weeks. Although no major spleen size reductions (SVR35) were seen at 6 months (expected given the monotherapy setting), these results were considered promising signs of disease-modifying efficacy in a population with very limited options. These findings, presented at the American Society of Haematology (ASH) meeting in December 2023, supported the transition to combination therapy.

Phase 2 Combination Trial with Ruxolitinib (2023 – present)

In December 2023, Syntara initiated a separate Phase 2 trial arm evaluating SNT-5505 in combination with ruxolitinib, following FDA clearance based on monotherapy data. The open-label study planned to recruit up to 15 patients across 19 clinical trial

sites in Australia, South Korea, Taiwan, and the US. Dosing involved SNT-5505 (200 mg BID) given on top of ruxolitinib for up to 12 months, with key endpoints including safety, symptom improvement, spleen volume reduction, and fibrosis changes.

Phase 2 interim data reported in Dec 2024 also showed promising signs: strong symptom score reduction and tolerability.

Patients in the trial demonstrated significant and sustained improvements over time. At the 12-week mark, nearly half of the evaluable patients (6/13) achieved at least a 50% reduction in their Total Symptom Score (TSS50). Notably, this response rate improved substantially as the study progressed, with 80% of patients (4/5) reaching this threshold by 38 weeks, suggestive of the drug's increasing efficacy over time. Equally compelling were the reductions in spleen volume, a crucial measure of treatment success in myelofibrosis. By week 38, 30% of patients achieved a ≥25% reduction, while 20% attained a ≥35% reduction, demonstrating clinically meaningful benefits that compare favourably with existing therapies.

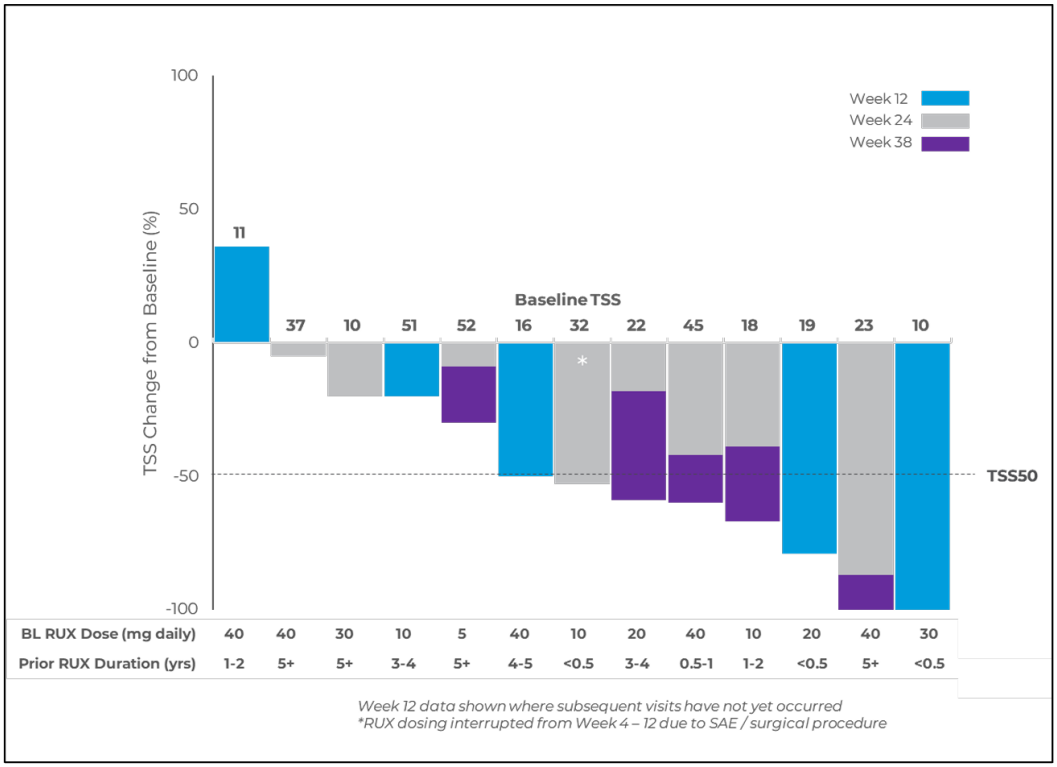

Figure 3: graph displaying the Total Symptom Score Change from Baseline (%) of each patient evaluated as part of the combination therapy arm of the Phase 2 clinical trial of SNT-5505 in MF. 8/13 patients (62%) reached TSS50 (a total symptom score reduction of 50%) up to week 38. The graph also shows TSS improvement despite RUX duration of 2+ years. Note that at time of interim data collection, not all patients had reached 38 weeks – only 5/13 had.

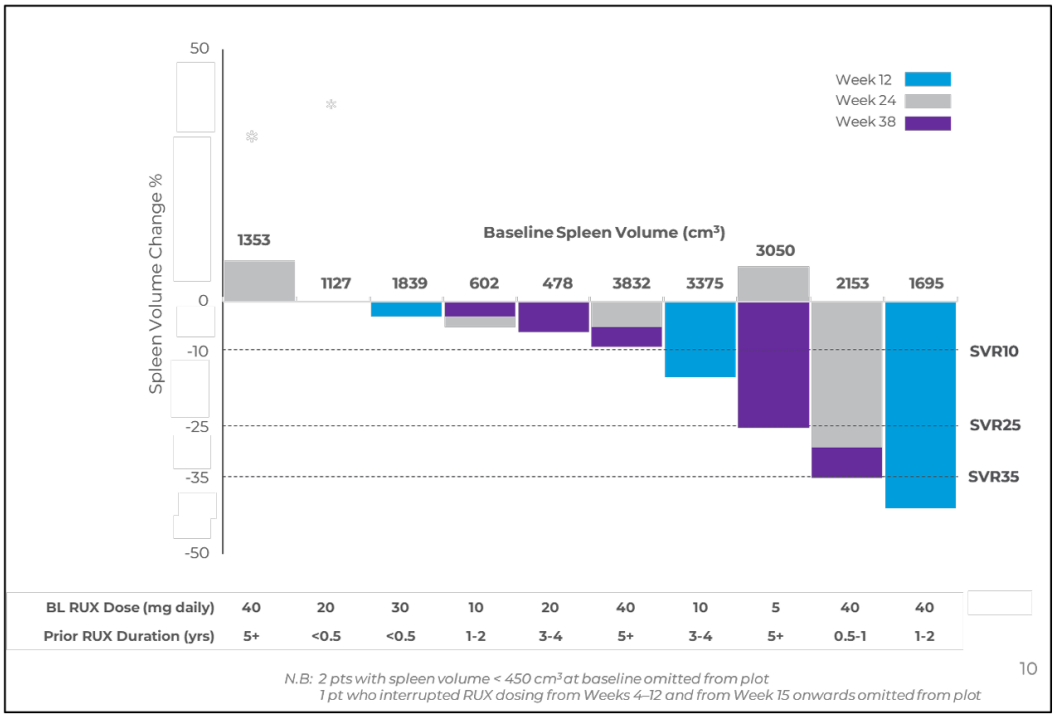

Figure 4: graph displaying Spleen Volume Change (%) of each patient evaluated as part of the combination therapy arm of the Phase 2 clinical trial of SNT-5505 in MF. 9/11 (82%) patients had either stable or reduced spleen volume.

There is strong evidence so far that SNT-5505 may have a sustained and progressively therapeutic effect. Though further data is required to validate this, it is great support to the value proposition of the treatment.

A key highlight of the interim data was the sustained and progressively improving therapeutic impact of SNT-5505. Unlike many existing treatments that reach a plateau, patients receiving SNT-5505 continued to experience ongoing enhancements in symptom relief and spleen volume reduction well beyond the initial response period. This indicates that the drug may provide a lasting disease-modifying benefit rather than merely offering temporary symptom control.

The safety profile of SNT-5505 was another key differentiator, with the treatment proving well-tolerated and no treatment-related serious adverse events reported. Haematological parameters, including haemoglobin levels and platelet counts, remained stable across the patient cohort, and even transfusion-dependent individuals experienced notable improvements, including a 70% reduction in transfusion requirements for one patient.

These promising results set the stage for the next phase of SNT-5505's development. With final Phase 2 data expected in the second half of 2025, Syntara is preparing for discussions with the FDA regarding the design of a pivotal Phase 2c/3 registration study. At the same time, the company is actively engaging with potential global and regional partners to accelerate the drug's path to commercialisation, reinforcing its position as a leader in extracellular matrix-targeting therapies.

Key Data Takeaways

- TSS50 (≥ 50% improvement in symptoms): achieved in 8/13 patients (62%)
    - 6/13 (46%) at week 12
    - 2/8 (25%) at week 24
    - 4/5 (80%) at week 38
- SVR35 (≥ 35% reduction in spleen volume): achieved in 2/10 patients
    - 9/10 patients had a stable or reduced spleen volume
    - 3/10 patients achieved > 25% reduction

Click here to jump to comparison of peers.

Pathway to Commercialisation

SNT-5505 has already achieved Orphan Drug Designation (ODD) from the FDA. ODD comes with several key benefits including 7 years of market exclusivity, tax credits for clinical trial costs and other beneficial incentives.

SNT-5505 has already achieved a significant regulatory milestone by obtaining Orphan Drug Designation (ODD) from the U.S. Food and Drug Administration (FDA). This designation is granted to drugs that are intended to treat rare diseases affecting fewer than 200,000 people in the United States. The purpose of the Orphan Drug program is to incentivise the development of treatments for conditions that would otherwise be overlooked due to limited commercial viability. By securing ODD, Syntara is eligible for several key benefits, including seven years of market exclusivity in the United States upon regulatory approval, tax credits for clinical trial costs, eligibility for FDA grants, and potential exemptions from certain regulatory fees. This designation not only strengthens SNT-5505's competitive positioning but also provides a streamlined regulatory pathway that could facilitate an expedited approval process.

Beyond the United States, Syntara is likely to consider global regulatory pathways to expand market access. The company is actively exploring opportunities in other key regions such as Europe and Australia, where regulatory frameworks for orphan drugs provide similar incentives to the FDA's program. SNT-5505's Orphan Drug Designation could also facilitate a priority review process in certain jurisdictions, potentially accelerating its approval timeline.

As part of its broader commercialisation strategy, Syntara may seek strategic partnerships or licensing deals with major pharmaceutical companies. These partnerships could provide additional funding, development support, and commercial expertise to enhance the drug's market entry. The company has indicated interest from industry players in the MF space, which could support late-stage trials and eventual commercial launch.

Syntara is also laying the groundwork for potential expansion of SNT-5505 into additional indications beyond myelofibrosis. The Company is focusing on myelodysplastic syndrome (MDS), a group of blood cancers with limited treatment options. Two new Phase 1c/2 trials in MDS are expected to begin in the first half of 2025, broadening the scope of SNT-5505's therapeutic potential and increasing its commercial value.

What Matters Most – Section 2

- ✓ **Disease-modifying potential – unlike Jak inhibitors that primarily alleviate symptoms, SNT-5505 directly targets the fibrotic process in MF – offering a genuine opportunity to alter disease course rather than merely manage it.**
- ✓ **Compelling Phase 2 Data – interim results show 80% of patients achieving TSS50, along with sustained spleen volume reductions. And the observed improvement trajectory continues over time, rather than plateauing.**
- ✓ **Favourable Safety Profile – SNT-5505 has so far demonstrated a clean safety profile with no SAEs to date. This positions the molecule as an attractive partner in combination regimens (i.e. alongside Ruxolitinib) and broadens its potential patient reach.**
- ✓ **Lucrative Addressable Market – the MF treatment market is estimated at US$2.5b and is expected to grow as improved diagnosis increases yearly incidence.**

3. Myelodysplastic Syndrome: An Additional Indication for SNT-5505

An Overview

Myelodysplastic syndromes are a group of rare blood cancer that arise from abnormalities in bone marrow. As with MF, current treatment options only offer modest benefits, with continued disease progression common.

Myelodysplastic syndromes (MDS) are a group of rare and complex blood cancers that arise from abnormalities in the bone marrow, leading to ineffective blood cell production. These disorders are characterised by dysplastic (abnormally developed) and inefficient haematopoiesis, which results in low blood cell counts (cytopenias) and a high risk of progression to acute myeloid leukemia (AML). Patients with MDS typically suffer from chronic anaemia, recurrent infections, and increased bleeding due to the bone marrow's inability to produce sufficient healthy red blood cells, white blood cells, and platelets. The condition is most prevalent in older adults, with the median age of diagnosis being around 70 years. Given the ageing global population, the incidence of MDS is expected to rise, further increasing the burden of this disease on healthcare systems.

Despite being a relatively rare condition, MDS represents a significant unmet medical need. Current treatment options, such as HMAs like azacitidine and decitabine, offer only modest benefits, with many patients experiencing disease progression or relapse. Furthermore, a large proportion of patients are ineligible for stem cell transplantation, which is the only potentially curative option but is rarely feasible due to the advanced age and frailty of most MDS patients. As a result, there is a pressing demand for novel therapies that can improve survival and quality of life for these patients. Research by Delveinsight suggests US incidence of MDS in 2023 was around 21,000 patients and is expected to grow in the years ahead. Prevalence estimates vary though most sources point to current US prevalence at approximately 100,000 people. The total addressable market for MDS treatments is estimated to exceed USD 6.64 billion by 2030, driven by the lack of effective long-term treatment options and the increasing prevalence of the disease. This makes MDS not only a high-impact area for drug development but also a commercially attractive opportunity for pharmaceutical innovation.

Not Just a One-Trick-Pony: SNT-5505 & Its Potential in MDS

SNT-5505 may have strong applicability in high-risk MDS patients – excessive fibrosis is a feature of MDS. Inhibiting LOX could reverse or slow down fibrosis, improving the bone marrow environment, allowing for the production of healthy blood cells.

Given the biological similarities between MDS and MF – particularly the role of fibrosis and aberrant ECM remodelling in the bone marrow microenvironment – Syntara has identified SNT-5505 as a strong candidate for treating high-risk MDS. Like MF, MDS is associated with dysregulated bone marrow stroma, excessive fibrotic signalling, and impaired haematopoiesis, all of which contribute to disease progression and poor patient outcomes.

By inhibiting LOX, SNT-5505 has the potential to reverse or slow down fibrosis, thereby improving the bone marrow environment and enhancing the production of healthy blood cells. This could translate into meaningful clinical benefits, including reduced transfusion dependency, improved haemoglobin levels, and better overall survival rates for MDS patients. Given the strong mechanistic rationale and the promising data emerging from the MF clinical program, Syntara is now moving forward with two planned Phase 1c/2 trials in MDS, one for low/intermediate-risk patients and another for high-risk patients, with recruitment expected to commence in the first half of 2025.

Clinical Focus

The low-to-intermediate-risk study will be conducted in Australia and aims to evaluate SNT-5505 in combination with existing standard-of-care therapies to assess its ability to improve haematopoiesis and reduce disease burden. Syntara has received funding support from the Australian government in the form of an Australian Medical Research Future Fund Grant for A$0.83 million.

Syntara is conducting two Phase I/II trials of SNT-5505 in MDS this year.

Meanwhile, the high-risk MDS trial, known as the AZALOX trial, will take place in Germany and is backed by a A$2.5 million grant from Deutsche Krebshilfe (German Cancer Aid). This study will be conducted across 7 specialist centres under the guidance of the German MDS Study Group and will begin with a dose-escalation phase, where up to 12 patients will receive two different doses of SNT-5505 in combination with 5-azacitidine over 6 months. Following this, an expansion phase will enrol 30 additional patients, who will receive the selected optimal dose of SNT-5505 alongside 5-azacitidine for another 6 months.

The primary endpoints of both studies will include safety, and tolerability, with additional secondary endpoints focusing on transfusion dependency reduction, haematological parameters, and quality of life. Syntara will supply the drug for both trials, and data from these studies will be used to inform future pivotal trial design and potential regulatory discussions for MDS. The trials are expected to commence recruitment in the first half of 2025, representing a major step forward in SNT-5505's expansion into additional haematological malignancies.

Attribute	Australian Phase 1c/2 Study	AZALOX German Phase 1b/2 Study
Phase	1c/2	1b/2
Indication	Low/Intermediate-Risk MDS	High-Risk MDS & CMML
Sponsor/Collaborators	Syntara, University of Newcastle, Australasian Leukaemia and Lymphoma Group	University Medical Center Mannheim, Syntara
Trial Sites	Australia	Germany
Design	Open-label, dose escalation followed by expansion	Dose escalation followed by expansion
Dosing Regimen	SNT-5505 + hypomethylating agent (5-azacitidine)	SNT-5505 + 5-azacitidine
Primary Endpoints	Safety and tolerability	Safety, tolerability, and optimal dosing
Secondary Endpoints	Transfusion dependency reduction, haematological parameters, quality of life	Haematological response, disease progression
Start Date	H1 2025	H1 2025

Figure 5: table outlining the two upcoming phase I/II trials of SNT-5505 in MDS.

Commercial Potential

The commercial potential of SNT-5505 in MDS is substantial, as existing treatments fail to address the underlying pathology of the disease. Most available therapies focus on modifying epigenetic regulation or providing symptomatic relief rather than targeting the structural abnormalities in the bone marrow that drive disease progression. If SNT-5505 demonstrates a disease-modifying effect in MDS, similar to what is being observed in MF, it could position itself as a first-in-class therapy for fibrosis-driven haematological malignancies. Furthermore, since MDS is often a precursor to AML, success in this indication could open avenues for SNT-5505's expansion into additional blood cancers, creating a broader pipeline of therapeutic opportunities.

4. The Competitive Landscape for SNT-5505

The success of SNT-5505 hinges on its ability show outperformance in spleen volume reduction (SVR) and Total Symptom Score (TSS) measures, while also having a better safety and tolerability profile. SVR35 refers to SVR reducing by 35% or more. TSS50 refers to TSS improving by 50% or more. Examples of key data points include:

- Percentage of patients reaching SVR35/TSS50 at week 24.
- Percentage of patients reaching SVR35/TSS50 at any time during the trial period.
- Median time to SVR35/TSS50.

More specifically, success as an MF monotherapy requires outperformance of Ruxolitinib (Rux). We don't expect Syntara to pursue this path in the near term, rather focusing on developing SNT-5505 as a combination therapy with Rux. Success in this pursuit requires outperformance of peers indicated as combination therapies with Rux.

This section discusses the existing treatments and treatments in development for MF and compares Syntara's recently announced interim Phase 2 results to Phase 2 and Phase 3 results (where applicable) of the peer group.

JAK Inhibitors for MF Treatment

Ruxolitinib, which received FDA approval in 2011, is the best-in-class treatment for MF.

In the therapeutic landscape of MF, JAK inhibitors have been instrumental in managing disease symptoms and progression. The primary agents in this class include ruxolitinib, fedratinib, pacritinib, and momelotinib. Each of these therapies has a unique development history, efficacy profile, and set of challenges, which are crucial to understand when evaluating emerging treatments like Syntara's SNT-5505.

Ruxolitinib (Jakafi/Jakavi)

Ruxolitinib, a JAK1/JAK2 inhibitor, received FDA approval in 2011, marking a significant milestone as the first JAK inhibitor for MF treatment. Its approval was based on the pivotal COMFORT-I and COMFORT-II trials. In COMFORT-I, 41.9% of patients achieved a SVR35 at week 24, compared to 0.7% in the placebo group. TSS50 was achieved in 45.9% of patients on-drug compared to 5.3% in the placebo group. COMFORT-II demonstrated similar efficacy, with 28.5% of patients achieving SVR35 at week 48, versus 0% with the best available therapy. Despite these benefits, long-term data indicate that approximately 75% of patients discontinue ruxolitinib within five years due to factors such as disease progression, cytopenias, or loss of response. Notably, grade 3/4 anaemia occurred in 31% of patients, and Thrombocytopaenia in 34.2%, potentially limiting its use in patients with low blood counts. The survival benefit associated with ruxolitinib has been a subject of discussion, with some studies suggesting improved outcomes, while others indicate the need for further research to confirm its impact on overall survival.

Fedratinib (Inrebic)

Fedratinib, a selective JAK2 inhibitor, was approved by the FDA in August 2019 for patients with intermediate-2 or high-risk primary or secondary MF. The JAKARTA-1 trial was instrumental in its approval, showing that 36% of patients achieved SVR35 at week 24, compared to 1% in the placebo group. Results from the JAKARTA-2 phase 2 trial reinforced strong efficacy. It involved patients previously treated with Rux or intolerant to Rux. SVR35 at week 24 was achieved in 55% of patients. SVR35 at week 12 was achieved in 47% of patients, suggesting the potential for strong early efficacy. Fedratinib offers an alternative for patients who are intolerant to or have relapsed after ruxolitinib therapy. However, its development faced challenges; in 2013, clinical trials were halted due to concerns about potential cases of Wernicke's encephalopathy. After a thorough review, the FDA lifted the clinical hold in 2017, leading to its eventual approval. Common adverse effects include gastrointestinal symptoms such as nausea and diarrhea, and there remains a boxed warning regarding the risk of serious and fatal encephalopathy, underscoring the need for careful patient monitoring.

Pacritinib (Vonjo)

Pacritinib is notable for its safety profile in patients with severe Thrombocytopaenia (platelet counts <50,000/μL), a group for whom other JAK inhibitors may be unsuitable. The PERSIST-2 phase 3 trial demonstrated that 18% of all on-drug patients achieved a SVR35 at week 24 with pacritinib, compared to 3% with the best available therapy, which included ruxolitinib. Those on drug were split into two dosing groups – (i) 400mg once daily and (ii) 400mg twice daily. In the latter cohort, SVR35 at week 24 was 22%. PERSIST-2 built on PERSIST-1, a preceding phase 3 trial of 327 patients that showed SVR35 at week 24 of 19% (vs 5% placebo, which in this case was best

available therapy). Pacritinib received FDA approval in February 2022 specifically for MF patients with low platelet counts. Despite its benefits, gastrointestinal side effects such as diarrhea are common, and careful patient selection and monitoring are advised. The development of pacritinib underscores the ongoing need for therapies tailored to specific patient subgroups within the MF population.

Momelotinib (Ojjaara)

Approved by the FDA in September 2023, momelotinib distinguishes itself by targeting JAK1/JAK2 and activin A receptor type I (ACVR1), addressing both splenomegaly and MF-associated anaemia. The phase 3 SIMPLIFY-1 trial (involving patients who had not previously been treated with a JAK inhibitor) had two arms: one with patients taking momelotinib, the other with patients on ruxolitinib). The data demonstrated non-inferiority to ruxolitinib in achieving a SVR35 at week 24 (26.5% vs. 29.0%, respectively). Moreover, it did not meet non-inferiority criteria for symptom improvement, with a TSS50 observed in 28.4% of momelotinib-treated patients compared to 42.2% with ruxolitinib. On the positive side, fewer patients who received momelotinib were transfusion dependent at week 24 suggesting it provides improvements in haemoglobin levels. The development journey of momelotinib highlights the complexities of addressing multiple facets of MF, including anaemia and splenomegaly, and the importance of a multifaceted therapeutic approach.

Drug		Ruxolitinib	Fedratinib	Pacritinib	Momelotinib
FDA Approval		2011	2019	2022	2023
JAK Inhibition		JAK1/JAK2	JAK2	JAK2/IRAK1	JAK1/JAK2
Phase 2 Results	Trial	Monotherapy	Monotherapy – prior rux treatment	Monotherapy	Monotherapy
	SVR35 (24wks)	41.9% (vs 0.7%)	55%	31%	N/A
	TSS50 (24wks)	49.5% (vs 5.3%)	26%	48.4%	N/A
	Other	44% achieved 'objective response' (≥50% reduction in palpable splenomegaly within 3 months)	SVR35 week 12 achieved in 47%	SVR35 up to treatment termination in 42.3%	48% achieved spleen response
Phase 3 Results	Trial	Monotherapy – "COMFORT"	Monotherapy – 2 dosing arms – "JAKARTA"	Monotherapy – two dosing arms – "PERSIST"	Monotherapy – mom vs rux – "SIMPLIFY-1"
	SVR35 (24wks)	28.5%	40% (vs 1%)	22% (vs 3%)	26.5% (vs 29% rux)
	SVR35 anytime	42.2%	N/A	N/A	N/A
	TSS50 (24wks)	N/A	34% (vs 7%)	32% (vs 14%)	28.4% (vs 42.2% rux)
	Other	97.1% of patients experienced clinical benefit with some degree of SVR	Only 2 of 97 patients on 500mg fed didn't see a decrease in SVR	Patients with prior rux: SVR35 in 13% vs 3%, TSS50 32% vs 15%	Transfusion dependence at wk24 (30.2% vs 40.1% rux)
	Discontinuation	11% at 24 weeks (vs 26% placebo); 14% at 24 weeks (vs 70% placebo)	400mg – 25% 500mg – 33% Placebo – 40%	Low dose – 14%, higher dose – 9%, palcebo	18.6% (vs 7.4% rux)
Safety		Anemia (45% grade 3-4 in COMFORT-1), Thrombocytopaenia (13% grade 3-4), some immunosuppression, infections; overall well-characterized AE profile with comparability in SAEs between drug and placebo cohorts.	Anaemia, Thrombocytopaenia, GI events (N/V/D), mild–moderate LFT elevations, and infections. Wernicke encephalopathy (noted at 500 mg) in patients with risk factors. Mortality from AEs: ~1%–4%.	Thrombocytopaenia (15-20% grade 3-4, especially common in low-platelet MF), diarrhea (55-60%), risk of bleeding; GI events frequent	92.1% (vs 95.4% rux) had 1 or more AE; 35.5% (vs 43.5% rux) had grade ≥ 3 AE inc. anaemia, Thrombocytopaenia, diarrhea, hypertension, neutropenia
Use Case		First-line for intermediate/high-risk MF	Second-line for rux-inadequate response/intolerance	Second-line (especially in severe Thrombocytopaenia)	Second-line or in MF with significant anemia/transfusion-dependence

Figure 6: table comparing the incumbent marketed therapies for MF. The table outlines phase 2 data and phase pivotal phase 3 data prompting NDA and ultimately FDA approval. various sources. The data highlights that SNT-5505 must achieve strong SVR35 and TSS50 to show clinical utility relative to the established, marketed therapies.

Comparison with SNT-5505

If SNT-5505 can display strong TSS50 and SVR35 data (alongside a strong safety profile) in the phase 2 topline data readout, further clinical development and commercial viability are further de-risked.

While JAK inhibitors have been instrumental in managing myelofibrosis (MF), they primarily address symptom control and spleen volume reduction rather than targeting the underlying disease pathology. Ruxolitinib, despite being the first-line treatment, sees a significant proportion of patients discontinue therapy within five years due to cytopenias and disease progression. Fedratinib, though useful for ruxolitinib-intolerant patients, carries risks such as Wernicke's encephalopathy, necessitating careful monitoring. Pacritinib, while filling a critical gap for thrombocytopenic patients, has a lower spleen response rate compared to ruxolitinib. Momelotinib offers a differentiated approach by addressing anaemia in addition to spleen volume, but it has not demonstrated superior symptom control when compared to ruxolitinib.

SNT-5505 distinguishes itself by addressing the fibrotic nature of MF rather than just modulating JAK-STAT signaling. As a pan-lysyl oxidase (LOX) inhibitor, it actively remodels the bone marrow microenvironment, a feature that none of the JAK inhibitors achieve. As discussed in section 2, interim Phase 2 data for SNT-5505, in combination with ruxolitinib, has shown promising sustained efficacy, with 46% of evaluable patients achieving ≥50% reduction in Total Symptom Score (TSS50) at 12 weeks, improving to 80% at 38 weeks – higher than what has been observed with any single-agent JAK inhibitor. Spleen volume reduction (SVR) rates, while lower than ruxolitinib in the short term (20% achieving SVR35 at 38 weeks), have demonstrated a continued trend of improvement over time. Unlike JAK inhibitors, where response rates plateau or decline, the ongoing trajectory of efficacy in SNT-5505-treated patients suggests a potential for longer-term disease modification rather than transient symptom relief.

Safety remains a key differentiator. JAK inhibitors are associated with dose-limiting cytopenias, whereas SNT-5505 has thus far maintained stable haematologic parameters in trial patients, with no treatment-related serious adverse events reported. Given that anaemia is a major reason for JAK inhibitor dose reductions or discontinuations, SNT-5505's ability to maintain stable hemoglobin levels while enhancing JAK inhibitor efficacy makes it an attractive potential adjunct or alternative therapy.

As MF treatment shifts towards combination regimens and therapies with disease-modifying potential, SNT-5505's mechanism offers a complementary or alternative strategy beyond symptom control. If ongoing trials confirm its long-term benefits, it could redefine MF management, providing both sustained symptomatic relief and an intervention that directly targets the fibrotic process driving disease progression. To make a judgement on SNT-5505's clinical utility in combination with ruxolitinib, we must await phase 2 final data.

Alternative Approaches to MF

New myelofibrosis therapies like navitoclax, pelabresib, navtemadlin, and parsaclisib show promise but face efficacy or safety challenges. SNT-5505 stands out for its potential to redefine treatment, pending proof of strong efficacy when combined with ruxolitinib.

Beyond JAK inhibitors, several novel therapeutic approaches for myelofibrosis (MF) have emerged, each targeting distinct pathways. These therapies, currently in late-stage development, aim to address the limitations of JAK inhibitors, which provide symptomatic relief but do not significantly alter the disease course.

Navitoclax

Navitoclax is a BCL-2/BCL-XL inhibitor developed by AbbVie. By inhibiting anti-apoptotic proteins, navitoclax selectively promotes the death of malignant cells in MF. The drug has completed patient enrolment in a Phase 3 trial, with results pending regulatory submission. In earlier trials, navitoclax demonstrated adequate efficacy with 30% of patients having achieved a ≥35% SVR35 at week 24. However, the trial did not meet TSS50 endpoints and the therapy is associated with significant toxicity, particularly Thrombocytopaenia, which was observed in 56% of patients at

grade 3/4 severity. Additionally, 32% of patients developed anaemia, and dose adjustments were required in 76% of cases. This high level of haematologic toxicity presents a substantial challenge to broader adoption, as it necessitates frequent monitoring and dosage modifications. From a regulatory perspective, the FDA is likely to scrutinize the drug's risk-benefit profile, particularly given the inadequate symptom score reduction.

Pelabresib

Pelabresib, an epigenetic BET inhibitor developed by MorphoSys and now in the hands of Novartis, takes a different approach by targeting transcriptional regulators involved in cytokine signalling. Initial excitement surrounding the drug stemmed from its potential to modify disease biology rather than just providing symptomatic relief. However, its Phase 3 trial (MANIFEST-2) failed to meet primary endpoints, significantly dampening expectations. In earlier Phase 2 studies, pelabresib showed moderate efficacy, with 37% of patients achieving TSS50 at 24 weeks and 20% achieving SVR35 at 48 weeks. However, its effects were inconsistent over time, and it demonstrated a relatively high rate of gastrointestinal toxicity, including diarrhoea (35%), nausea (24%), and abdominal pain (23%). Additionally, an increased rate of blast-phase transformation was reported, raising concerns about its long-term safety. The regulatory outlook for pelabresib is now uncertain, as the FDA is unlikely to approve the drug without additional combination data that demonstrates a survival benefit. Commercially, MorphoSys faces significant challenges in securing a foothold in the MF treatment landscape, as pelabresib's efficacy does not appear to be sufficient to justify its side effect burden or to provide a compelling advantage over existing therapies.

Navtemadlin

Another candidate in this space is navtemadlin (also referred to as KRT-232), an MDM2 inhibitor designed to restore p53 function – a critical tumor suppressor pathway frequently dysregulated in myelofibrosis (MF). Kartos Therapeutics has explored navtemadlin in multiple settings:

- **Phase 2 in R/R MF:** In patients relapsed or refractory (R/R) to JAK inhibitors, a completed phase 2 trial reported SVR35 achieved in 15% of patients (vs 5% among those treated with best available therapy – 'control') and TSS50 achieved in 24% (vs 12% in control group) at 24 weeks. Gastrointestinal (GI) toxicity was pronounced in this study, with 64% of patients experiencing diarrhea and 68% experiencing nausea, necessitating aggressive prophylactic management. Haematological toxicities did occur but appeared somewhat less severe than those observed with navitoclax.

- **Phase 2 in JAK inhibitor-naive MF:** Kartos has also completed a separate phase 2 trial in patients who had not previously received JAK inhibitors. We await results from this trial.

- **Phase 1b/2 of navtemadlin + ruxolitinib:** A combination phase 1b/2 trial with navtemadlin plus ruxolitinib in patients with primary or secondary TP53 wild-type myelofibrosis who experienced suboptimal response to ruxolitinib alone. The trial showed that among evaluable patients, SVR35 at week 24 was 32% and TSS50 of 32%. These results are clinically meaningful.

- **Ongoing Phase 3 in suboptimal responders to ruxolitinib:** Kartos has now initiated a pivotal phase 3 trial investigating navtemadlin in patients who have demonstrated a suboptimal response to ruxolitinib. ClinicalTrials.gov estimates the primary completion (i.e. topline data) will be by the end of 2026.

The regulatory outlook for navtemadlin depends heavily on whether it can demonstrate long-term survival benefits and a tolerable safety profile. Without a

clear differentiation in either efficacy or safety, it may struggle to gain traction in an increasingly competitive landscape.

Parasaclisib

Parsaclisib, a potent and highly selective phosphatidylinositol 3-kinase delta (PI3K) inhibitor, has shown promise in MF treatment, particularly for patients with suboptimal response to ruxolitinib. In a phase 2 study, parsaclisib added to stable-dose ruxolitinib demonstrated efficacy in reducing spleen volume and improving symptoms in MF patients. The combination therapy showed manageable toxicity, with the most common adverse events being nausea, diarrhea, and fatigue. Notably, the addition of parsaclisib maintained steady hemoglobin levels, addressing a common concern with MF treatments. While parsaclisib has shown efficacy in other hematological malignancies, its development for MF faced a setback when the phase 3 LIMBER-304 trial was discontinued due to the unlikelihood of meeting its primary endpoint.

SNT-5505 stands out among the current pipeline therapies due to its superior symptom improvement, progressive spleen volume reductions, and favourable safety profile. While navitoclax and navtemadlin offer reasonable efficacy, their severe toxicities present substantial limitations. Pelabresib, once viewed as a promising disease-modifying therapy, has failed to meet expectations in clinical trials. With its unique mechanism of action and strong early data, SNT-5505 has the potential to redefine the treatment paradigm for MF and secure a strong competitive position in the market. As already stated, the key for SNT-5505 is to prove its strong safety profile is paired with strong efficacy when dosed alongside ruxolitinib. The commercial viability of SNT-5505 relies on strong efficacy, and most likely, efficacy beyond that of the incumbent and emerging peers.

Drug		**Pelabresib**	**Navitoclax**	**Navtemadlin**	**Parsaclisib**
Company		MorphoSys	AbbVie	Kartos	Incyte
MOA		BET Inhibitor	BCL-2/BCL-XL inhibitor	MDM2 inhibitor	PI3K inhibitor
Status		Phase 3 Complete	Phase 3 Complete	Ongoing Phase 3	Ongoing Phase 3
Phase 2 Results	Trial	Combination with Rux (>2 months duration) – "MANIFEST"	Combination with Rux (>3 months duration) – "REFINE"	Combination with Rux	Combination with Rux (>6 months duration)
	SVR35 (24wks)	57/84 (68%)	26.5%	16%	31%*
	SVR35 anytime	57/84 (68%)	41% (median 13.8 mths)	N/A	41%*
	TSS50 (24wks)	46/82 (56%)	30%	30%	33.3%*
	Other	36% saw improved haemoglobin levels, 28% saw ≥ 1 grade improvement in fibrosis	46% achieved TSS50 at any time in trial	Disease-modifying activity: at 24 wks, patients experienced a -70% change in CD34+ cells from baseline vs -38% among control group.	TSS50 at week 42 was 46.7% in high-dose cohort suggesting greater symptom improvement with longer duration
Phase 3 Results	Trial	Combination with Rux	Combination with Rux	Combination with Rux	Combination with Rux
	SVR35 (24wks)	66% (vs 35% Rux + placebo)	63.2% (vs 31.5% Rux + placebo)	Trial commenced mid-2024	55.3% (vs 45.7% rux & placebo)
	SVR35 anytime	N/A	77% (vs 42% Rux + placebo)		N/A
	TSS50 (24wks)	52% (vs 46% Rux + placebo)	N/A		34.8% (vs 39.2% rux & placebo)
	Other	Both SVR35 & TSS50 in 40.2% (vs 18.5% Rux + placebo)	TSS mean change -9,7 (vs -11.1 in Rux + placebo)	N/A	Equivalent time to onset of SVR35 (88 days vs 92 days placebo)
Safety		Anaemia – 35% Thrombocytopaenia – 12%; grad 3+ AEs in 55% of patients	Thrombocytopaenia (88%), anaemia, diarrhea, neutropenia. SAEs experienced in 26% of patients.	GI toxicity common in the phase 2 as well as grade ¾ thrombocytopaenia	60% on-drug had grade 3 or higher AE (vs 57.5% placebo); GI events common
Outlook		Primary and secondary endpoints met; uncertainties on regulatory approval timeline though	Primary endpoint met, but secondary endpoint not met; company engaging with regulatory authorities	Regarded as potentially disease-modifying; phase 3 readout sometime in 2026	Ongoing phase 3 with no definitive regulatory timeline, though early data suggests longer

	guidance by Novartis CEO for 2027	lasting symptom improvement

Figure 7: table comparing the therapies in development for MF. sourced from various publications. note that the phase 2 data points for parsaclisib are taken from the higher-dosed arm of the trial. Phase 3 data on parsaclisib is interim data.

MDS Treatment Landscape

The competitive landscape for myelodysplastic syndromes (MDS) is broad, with treatment approaches ranging from supportive care to targeted therapies designed to modify disease progression. Drugs indicated for MF have often been tested in MDS – pacritinib ('SB1518' in development) was had a phase 2 in MDS initiated in 2011, though, this trial was ultimately terminated. Current pharmacological interventions primarily focus on managing cytopenias, reducing transfusion dependence, and, in higher-risk patients, delaying progression to acute myeloid leukemia (AML).

The MDS treatment landscape includes hypomethylating agents like decitabine, lenalidomide for del(5q) patients, luspatercept for ring sideroblasts, and the recently approved imetelstat. Imetelstat is likely the best of the bunch due to its broader efficacy in lower-risk, transfusion-dependent MDS patients.

Decitabine

Hypomethylating agents (HMAs), including azacitidine and decitabine, remain the backbone of MDS treatment, particularly for intermediate- to high-risk cases. These agents inhibit DNA methylation, promoting re-expression of silenced tumour suppressor genes, leading to haematologic improvement. However, their benefits are often transient, with many patients developing resistance or experiencing disease relapse within a year of response initiation. Decitabine, which received FDA approval in 2006, has demonstrated modest overall response rates (~21%), but its lack of a consistent survival benefit limits its impact beyond delaying disease progression. While an oral decitabine/cedazuridine formulation has improved treatment accessibility (FDA-approved in 2020 and sold under the brand name Inqovi), the fundamental limitations of HMAs in MDS remain unchanged.

Lenalidomide

Lenalidomide has revolutionized treatment for lower-risk MDS patients with a deletion 5q cytogenetic abnormality, achieving transfusion independence rates of approximately 67% with a median response duration exceeding two years. However, its efficacy is significantly reduced in non-del(5q) MDS, limiting its broader role in the treatment landscape. Another key advancement in lower-risk MDS is luspatercept, an erythroid maturation agent approved in 2020 for patients with ring sideroblasts experiencing transfusion-dependent anaemia. While luspatercept significantly reduces transfusion burden (with ~37% achieving ≥ 8-week transfusion independence), its benefit is largely confined to the SF3B1-mutated subset of MDS, restricting its applicability to a narrower patient population.

Imetelstat

The most recent breakthrough in the treatment of lower-risk, transfusion-dependent MDS is imetelstat, a first-in-class telomerase inhibitor approved in 2024. By selectively targeting malignant progenitor cells, imetelstat has demonstrated superior transfusion independence rates compared to existing therapies (~40% achieving ≥8-week transfusion independence, with ~28% maintaining it for ≥ 24 weeks). Unlike luspatercept, which is predominantly effective in patients with ring sideroblasts, imetelstat has shown efficacy across a broader spectrum of lower-risk MDS patients, offering an important new treatment option for those who have lost response to erythropoiesis-stimulating agents (ESAs) and luspatercept. While requiring intravenous administration, its durable responses position it as a promising therapeutic innovation in a field with limited alternatives for transfusion-dependent patients.

	Decitabine	Azacitidine	Imetelstat	Luspatercept	Lenalidomide
Product	Dacogen	Vidaza	Rytelo	Reblozyl	Revlimid
Company	Johnson & Johnson	Celgene	Geron	Merck	Celgene
Indication	Higher-risk MDS	Higher-risk MDS	Lower-risk MDS (transfusion-	Lower-risk MDS (ring sideroblasts)	Lower-risk MDS (del(5q) cytogenetic abnormality)

			dependent anaemia)		
Line of Treatment	First	First	Second (after ESA failure)	Second (after ESA failure)	First for specific indication
Mechanism of Action	Hypomethylating agent – inhibits DNA methylation, restoring normal gene function	Hypomethylating agent – inhibits DNA methylation, restoring normal gene function	Telomerase inhibitor – targets malignant progenitor cells	Erythroid maturation agent – enhances RBC production	Immunomodulatory agent – modulates immune response and bone marrow microenvironment
FDA Approval Year	2006	2004	2024	2019	2005
Route of Administration	Intravenous (IV)	Subcutaneous (SC) or IV	IV	SC	Oral (capsule)
Treatment Schedule	5-7 day IV infusion every 4 weeks	Typically 7 days of SC/IV dosing every 4 weeks	IV infusion every 3-4 weeks	SC injection every 3 weeks	Oral daily until disease progression
Efficacy	Improves overall survival and response rates in higher-risk MDS patients	Improves overall survival in higher-risk MDS; reduces transfusion dependence	Achieves durable transfusion independence in a significant proportion of patients	Reduces transfusion burden, effective in ring sideroblast-positive patients	Reduces transfusion dependence in del(5q) MDS patients
Clinical Trial Results	~30–40% response rate in high-risk MDS; median survival ~20 months	~40–50% overall response rate; median survival ~24 months in higher-risk MDS (AZA-001 trial)	40% of patients achieved transfusion independence in Phase 3 trials	~38% transfusion independence in ring sideroblast patients	~67% transfusion independence in del(5q) MDS patients
Key Side Effects	Myelosuppression, fatigue, nausea, fever, infection risk	Myelosuppression, GI toxicity (nausea/vomiting), injection-site reactions	Thrombocytopaenia, neutropenia, liver enzyme elevation	Fatigue, hypertension, headache, diarrhea	Neutropenia, Thrombocytopaenia, rash, diarrhea
Limitations	Responses are often transient, with resistance developing in most patients	Requires multiple cycles; some patients do not respond or develop resistance; therapy may need to be continued long term	Potential for liver toxicity and myelosuppression	Limited efficacy in non-ring sideroblast patients; gradual onset of action	Limited to patients with del(5q) mutation; high risk of neutropenia and Thrombocytopaenia
Avg. Price p.a.	~US$100-120k	~US$100-120k	Not yet marketed	~US$130k	~US$120-130k

Figure 8: Comparison of five major therapies for myelodysplastic syndromes (MDS)—decitabine, imetelstat, luspatercept, lenalidomide, and azacitidine—highlighting their indications, line of treatment, mechanism of action, clinical trial results, key side effects, and annual cost estimates. Note that the Avg. Price p.a. for each drug is an estimate based on the best available information.

Emerging Therapies

The MDS therapeutic landscape is evolving rapidly, with research directed towards targeted therapies, drug combinations, and immunomodulatory treatments that aim to disrupt the core pathological processes in MDS and prevent relapse. Inhibitors focused on specific genetic mutations such as IDH1/2 remain of considerable interest, since they can tailor treatment to patients' unique molecular profiles. Additionally, combining hypomethylating agents (HMAs) with new classes of drugs – including immune checkpoint inhibitors, epigenetic modifiers, and monoclonal antibodies – is showing promise in extending response and deepening remissions.

Alongside these platforms, other new agents have entered clinical development. Venetoclax (AbbVie), an oral inhibitor of the BCL-2 protein, has had success in acute myeloid leukaemia (AML) when combined with HMAs, leading investigators to explore its potential in MDS. Early-phase studies indicate that the combination of Venetoclax with azacitidine or decitabine can enhance the depth of remissions in higher-risk MDS, partly through driving apoptosis of malignant progenitor cells. Multiple Phase 1 and Phase 2 trials have reported encouraging response rates and

manageable safety profiles, prompting broader evaluation in ongoing Phase 3 studies to refine dosing regimens and identify optimal patient subgroups.

Briquilimab is a monoclonal antibody targeting the c-Kit receptor (CD117) on haematopoietic stem and progenitor cells. Initially developed to enhance stem cell transplant conditioning, it is now being explored in a Phase 2 setting for higher-risk MDS. The rationale is to deplete the malignant clone more effectively while preserving enough healthy marrow function to support immune reconstitution. Emerging data suggest Briquilimab may reduce relapse post-transplant in MDS and improve the durability of remission—an outcome of particular value in patients with high-risk disease. Further trials are exploring safety, transplant outcomes, and whether adding Briquilimab to standard MDS regimens can expand the window for successful transplants.

Bringing it Back

Compared to existing and emerging therapies, SNT-5505 offers a fundamentally different approach by targeting the fibrotic processes within the bone marrow that contribute to disease pathology. Unlike HMAs, which primarily modulate gene expression, or agents like luspatercept and imetelstat, which focus on symptomatic improvement, SNT-5505 actively remodels the bone marrow microenvironment. This distinction is particularly important in MDS, where ineffective haematopoiesis and marrow fibrosis significantly impact treatment responses. Interim clinical data suggest that SNT-5505 has the potential to reduce transfusion dependence and improve blood counts, findings that align with its proposed mechanism of action.

Another key advantage is its safety profile. While HMAs and other systemic agents often lead to significant immunosuppression and haematologic toxicities, SNT-5505 has demonstrated stability in haematologic parameters without treatment-related serious adverse events. This could position it as an ideal candidate for combination therapy, particularly with existing HMAs, by enhancing efficacy without adding further toxicity.

The future of MDS treatment is shifting towards precision medicine, where therapies are tailored to both genetic and pathophysiologic disease characteristics. Given its novel mechanism and emerging data, SNT-5505 could redefine MDS management by addressing disease progression at its root cause, rather than merely controlling symptoms. If its long-term efficacy and safety continue to be validated, it has the potential to establish itself as a new standard in the evolving therapeutic landscape of MDS.

5. SNT-4728: Expanding Syntara's Innovation into Neurodegenerative Disease Treatment

Introduction

SNT-4728 represents an important extension of Syntara's pioneering work in targeting ECM dysfunction, reinforcing the company's leadership in the development of novel therapeutics for fibrosis and inflammation-driven diseases. Positioned within Syntara's broader pipeline, SNT-4728 is being developed as a potential best-in-class semicarbazide-sensitive amine oxidase (SSAO)/monoamine oxidase B (MAO-B) inhibitor, specifically targeting neuroinflammatory processes linked to Parkinson's disease (PD) and idiopathic REM sleep behaviour disorder (iRBD), a recognised precursor condition to neurodegenerative diseases such as PD.

Given Syntara's established expertise in oxidative enzyme inhibition through its development of SNT-5505 for haematological malignancies, the company is uniquely

positioned to leverage this platform in the neurodegeneration space. SNT-4728's mechanism of action is well-suited to addressing the chronic neuroinflammation observed in PD and iRBD. SSAO/MAO-B inhibition has been shown to modulate neuroinflammatory responses and reduce oxidative stress - both key contributors to neuronal degeneration in Parkinson's.

SNT-4728 is Syntara's promising SSAO/MAO-B inhibitor targeting neuroinflammation in Parkinson's disease and REM sleep behavior disorder, with early trials showing strong target engagement and safety profiles, currently in Phase 2 trials funded by Parkinson's UK.

Clinical development to date has progressed with promising outcomes. Early-stage trials have demonstrated the drug's ability to effectively engage its target while maintaining a strong safety profile, a critical factor in long-term neurodegenerative treatment strategies. SNT-4728 is being investigated in collaboration with Parkinson's UK, underscoring the significant interest in its potential to fill a major gap in current treatment options. Parkinson's UK is funding the current ongoing phase 2 trial. The compound's dual action as an SSAO and MAO-B inhibitor distinguishes it from existing PD therapies, which primarily focus on dopamine replacement rather than addressing upstream disease-modifying pathways.

Parkinson's Disease & Therapeutic Approaches

PD is a progressive neurodegenerative disorder primarily characterised by the loss of dopaminergic neurons in the substantia nigra, leading to debilitating motor dysfunction, cognitive decline, and a range of non-motor symptoms. Over the years, a variety of therapies have been developed to manage the symptoms of the disease, yet there remains no cure. The current therapeutic landscape includes pharmacological treatments, surgical interventions, and emerging disease-modifying approaches, each offering benefits but also presenting significant limitations.

Current Parkinson's treatments only manage symptoms, while Syntara's SNT-4728 uniquely targets the underlying neuroinflammation and oxidative stress driving the disease progression.

The cornerstone of PD treatment remains pharmacotherapy, with Levodopa (L-Dopa) standing as the most effective and widely used medication since its introduction in the 1960s. By replenishing depleted dopamine levels, Levodopa provides significant symptom relief, particularly in the early stages of the disease. However, long-term use is associated with motor complications such as dyskinesia (involuntary muscle movements), limiting its efficacy over time. To mitigate these complications, dopamine agonists like pramipexole, ropinirole, and rotigotine have been developed. These medications stimulate dopamine receptors directly and are often used either as monotherapy in early PD or in combination with Levodopa in later stages. While they offer a longer duration of action and fewer motor fluctuations, their use is frequently associated with psychiatric side effects, including impulse control disorders.

For patients with advanced Parkinson's who experience significant motor fluctuations despite optimal pharmacological treatment, deep brain stimulation (DBS) offers an alternative. This surgical procedure, which has been used clinically since the early 2000s, involves implanting electrodes in specific brain regions to modulate abnormal neural activity. DBS has been shown to significantly reduce tremors, rigidity, and bradykinesia while also decreasing reliance on medications. However, it is an invasive procedure with inherent surgical risks and does not address the non-motor symptoms or halt disease progression.

Beyond established treatments, considerable research is being conducted into novel therapies aimed at modifying the course of PD. Gene therapy represents a promising frontier, with experimental approaches focused on introducing genes that enhance dopamine synthesis or protect neurons from degeneration. While some trials have shown potential, challenges such as complex delivery mechanisms and long-term safety concerns remain. Similarly, stem cell-based therapies aim to replace lost dopaminergic neurons, though these approaches are still in the experimental phase and face significant technical and ethical hurdles.

Despite these advances, existing therapies primarily focus on symptom management rather than addressing the underlying mechanisms driving

neurodegeneration. This is where SNT-4728, developed by Syntara, represents a pioneering approach. Unlike conventional treatments that primarily target dopamine replacement or modulation, SNT-4728 is designed to tackle neuroinflammation and oxidative stress. It's mechanism of action offers a fundamentally different therapeutic angle compared to existing dopaminergic treatments.

The Rationale Behind SNT-4728's Development

Research shows blocking SSAO and MAO-B enzymes reduces brain inflammation and oxidative damage in Parkinson's disease, with studies showing dual inhibitors protect neurons and reduce inflammatory markers in lab models.

Extensive research has demonstrated that inhibition of SSAO and MAO-B play a critical role in modulating neuroinflammatory responses, which are key drivers of neurodegeneration in Parkinson's disease. SSAO is involved in the oxidative deamination of primary amines, leading to the production of toxic aldehydes, hydrogen peroxide, and ammonia – all of which contribute to oxidative stress and neuroinflammation. In studies from 2014 and 2021, elevated SSAO activity was detected in the brains of Parkinson's disease patients, correlating with increased gliosis and neurodegeneration. Similarly, MAO-B, an enzyme responsible for the degradation of dopamine, produces hydrogen peroxide as a byproduct, exacerbating oxidative damage in dopaminergic neurons, a process well-documented in studies exploring oxidative stress in Parkinson's pathology.

Preclinical studies have reinforced the therapeutic potential of dual SSAO/MAO-B inhibition. A study by Fülöp et al. (2018) demonstrated that SSAO inhibitors significantly reduced neuroinflammation in rodent models of neurodegeneration by decreasing microglial activation and lowering pro-inflammatory cytokine levels. Similarly, the neuroprotective effects of MAO-B inhibitors, such as selegiline and rasagiline, have been well established in both clinical settings. The 1993 DATATOP study showed that early treatment with selegiline delayed the need for levodopa therapy, supporting its role in reducing oxidative damage. More recently, studies have explored novel dual SSAO/MAO-B inhibitors, with evidence suggesting that their combined action leads to a synergistic reduction in neuroinflammatory markers and oxidative stress, enhancing neuronal survival in experimental Parkinson's models.

Clinical Development

Syntara's clinical development of SNT-4728 has progressed through rigorous early-stage trials, reinforcing its potential as a novel therapeutic for idiopathic REM sleep behaviour disorder (iRBD) and Parkinson's disease (PD). The drug has undergone a Phase 1 clinical trial designed to assess its safety, pharmacokinetics, and pharmacodynamics in healthy volunteers. This trial demonstrated excellent tolerability across multiple dosing cohorts, with no serious adverse events reported and a favourable pharmacokinetic profile that supports once-daily oral dosing. Importantly, the trial confirmed robust target engagement, with SNT-4728 achieving high levels of SSAO inhibition in plasma, a critical indicator of its potential efficacy in neuroinflammatory conditions.

Progression to Phase 2

SNT-4728 demonstrated strong safety in Phase 1 trials and is now in Phase 2 studies for REM sleep behaviour disorder, with results expected in 2025 that could establish it as the first therapy targeting neuroinflammation to prevent Parkinson's.

Building on these encouraging results, Syntara has advanced SNT-4728 into a Phase 2 study in collaboration with Parkinson's UK, investigating its potential to treat iRBD, a recognised prodromal stage of Parkinson's and other synucleinopathies. The study, enrolling patients with clinically diagnosed iRBD, aims to assess SNT-4728's effects on sleep architecture, neuroinflammatory biomarkers, and disease progression markers. Given that iRBD is strongly associated with the development of PD, with up to 80% of patients progressing to a neurodegenerative disorder within a decade, this study holds significant implications for early intervention strategies.

Preliminary data from the trial is anticipated in the second half of 2025, offering early insights into SNT-4728's effectiveness in reducing neuroinflammation, a key driver of PD progression. The final Phase 2 data readout is projected for late 2025 or early 2026,

which will be crucial in determining the drug's ability to slow disease progression in at-risk individuals. If the results are favourable, this could pave the way for a larger, registrational study, bringing SNT-4728 closer to becoming the first approved therapy to target neuroinflammation as a means of preventing Parkinson's.

6. SNT-6302 & SNT-9465: Innovating in Skin Scarring Treatment

Introduction

Skin scarring is a prevalent and often debilitating medical concern that arises from injuries, surgeries, or burns, leading to excessive fibrotic tissue formation. These scars can result in aesthetic, functional, and psychological burdens for patients, with current treatments offering limited efficacy in fully restoring normal skin structure and function. Syntara is at the forefront of addressing this challenge through its innovative topical pan-lysyl oxidase (pan-LOX) inhibitor, SNT-6302. This novel therapeutic has demonstrated significant improvements in scar vascularisation and extracellular matrix remodelling, bringing treated scars structurally and biologically closer to normal, uninjured skin. In March 2025, Syntara also announced a new program – SNT-9465 – aimed at improving the appearance physical properties of hypertrophic scars.

The Role of Pan-LOX Inhibitors in Treating Skin Scarring

Scar formation is driven by excessive extracellular matrix (ECM) deposition and cross-linking, primarily mediated by the LOX enzyme family. These enzymes catalyse the cross-linking of collagen and elastin fibres, which strengthens scar tissue and also makes it more rigid and structurally different from normal skin. While this process is beneficial in wound healing, excessive LOX activity leads to the formation of hypertrophic scars and keloids, which can impair skin flexibility, cause discomfort, and negatively impact appearance.

SNT-6302

SNT-6302 directly inhibits LOX enzymes, reducing their ability to reinforce collagen fibres through excessive cross-linking. This action helps to restore a more balanced collagen architecture, resulting in a softer, more pliable, and structurally normalised scar. The remodelling of the ECM facilitated by SNT-6302 not only improves skin texture and elasticity but also enhances its functional properties, making the treated skin more akin to normal, uninjured tissue.

SNT-6302 inhibits LOX enzymes to reduce collagen cross-linking in scars. The SOLARIA2 trial showed it was well-tolerated, reducing hydroxyproline levels by 30%, indicating scar remodelling, though visible improvements weren't apparent at three months.

Clinical Development

Advanced biochemical analyses from the SOLARIA2 clinical trial have provided compelling evidence supporting the efficacy of SNT-6302 in modifying established scar tissue. The Phase 1c, double-blind, placebo-controlled study, conducted at Fiona Stanley Hospital (Murdoch, Western Australia), enrolled 42 adult patients with scars older than one year and measuring at least 10 cm^2. Over a 12-week period, patients applied either SNT-6302 or a placebo cream three times per week, with the primary goal of assessing safety and tolerability. The treatment was well tolerated, showing no serious adverse events. Biochemical analyses of scar biopsies revealed a 30% reduction in hydroxyproline levels ($p<0.01$)—a surrogate marker of collagen content—relative to placebo. This finding supports the notion that SNT-6302 actively remodels scar tissue rather than merely altering its texture. Notably, while a mean 66% reduction in LOX activity was observed, no significant improvement in overall scar appearance was detected at the three-month mark, suggesting a need for longer-term assessments.

Trial	SOLARIA2 (Phase 1c)
Drug Investigated	SNT-6302 (Topical Pan-LOX Inhibitor)
Study Design	Double-blind, placebo-controlled
Trial Location	Burn Injury Research Unit, University of Western Australia & Fiona Wood Foundation
Number of Patients	42 adult patients
Inclusion Criteria	Patients with mature scars (>1 year old) and ≥10 cm^2 in size
Treatment Duration	3 months
Key Findings	**Vascularisation Improvement:** Significant increase in blood vessel density (p=0.03) indicating enhanced tissue regeneration. **Extracellular Matrix Remodelling:** Structural improvements in scar tissue (p=0.03). **Collagen Reduction:** 30% decrease in hydroxyproline levels (p<0.01), confirming reduced collagen deposition. **Collagen Cross-Linking:** Reduced mature collagen cross-linking, showing structural reversal of fibrosis.
Placebo Group Findings	No significant changes observed.
Safety Profile	No systemic safety concerns, well tolerated.
Conclusion	SNT-6302 significantly remodels long-standing scar tissue, suggesting potential for reversing fibrosis and restoring normal skin structure.

Table 2: able summarizes the key findings from the SOLARIA2 Phase 1c clinical trial investigating SNT-6302, a topical Pan-LOX inhibitor developed by Syntara. The study evaluated the drug's efficacy in treating mature scars in 42 adult patients over a 3-month treatment period. Results showed significant improvements in vascularization, ECM remodelling, and collagen reduction compared to placebo.

Advancing The Skin Scarring Program – SNT-6302 & SNT-9465

In 2025 and beyond, Syntara plans to expand its scar management pipeline by introducing SNT-9465, a next-generation topical anti-fibrotic drug designed for daily use with improved tolerability and efficacy. Building upon insights from SOLARIA2, which confirmed the strong potential of LOX inhibition in established scars, the company will initiate a Phase 1a/b clinical trial of SNT-9465 in Q2 2025. This study will first assess safety in healthy volunteers before moving to an open-label extension in hypertrophic scars, with results anticipated in the first half of 2026.

Meanwhile, Syntara will continue to investigate SNT-6302 in trials evaluating scar prevention particularly whether early application of pan-LOX inhibitors can curb excessive collagen cross-linking before a scar fully develops – alongside broader research in severe burns, keloid-prone skin, and surgical patients at higher risk of disfiguring scars. Both compounds may also be explored in combination with existing therapies (e.g., laser treatments, silicone sheeting, corticosteroid injections) to offer a more comprehensive approach to scar mitigation.

With strong clinical validation emerging, Syntara is engaging with global regulators, including the FDA, to chart a clear path toward approval and will consider streamlined pathways such as Fast Track or Breakthrough Therapy designations. In parallel, the company is pursuing commercialisation strategies – including potential strategic partnerships – to ensure these next-generation scar therapies reach the widest possible patient population.

The Market Opportunity: Addressing the Global Burden of Skin Scarring

Market Size, Dynamics & Trends

Growth in the global scar treatment market reflects the substantial demand for effective therapies. In 2023, the market was valued at approximately USD 26.50 billion and is projected to reach around USD 76.20 billion by 2034, growing at a compound annual growth rate (CAGR) of 10.05% during this period. This growth is driven by factors such as increasing aesthetic consciousness, a rise in the number of surgical procedures, and a higher incidence of skin injuries and burns resulting from, for

example, rising incidence of road accidents (50 million annually, per Population Reference Bureau), and burn injuries (1.1 million requiring medical attention in the U.S. annually, per CDC).

The U.S. scar treatment market alone was valued at USD 7.05 billion in 2023 and is estimated to reach around USD 20.44 billion by 2034, growing at a CAGR of 10.13% from 2024 to 2034. The topical treatment segment dominated the market, holding a 65.5% share in 2023. This is due to the widespread use of over-the-counter products like silicone sheets, gels, oils, ointments, sprays, and creams, which are directly applied to the skin to treat scars. SNT-6302 falls into this category of the market.

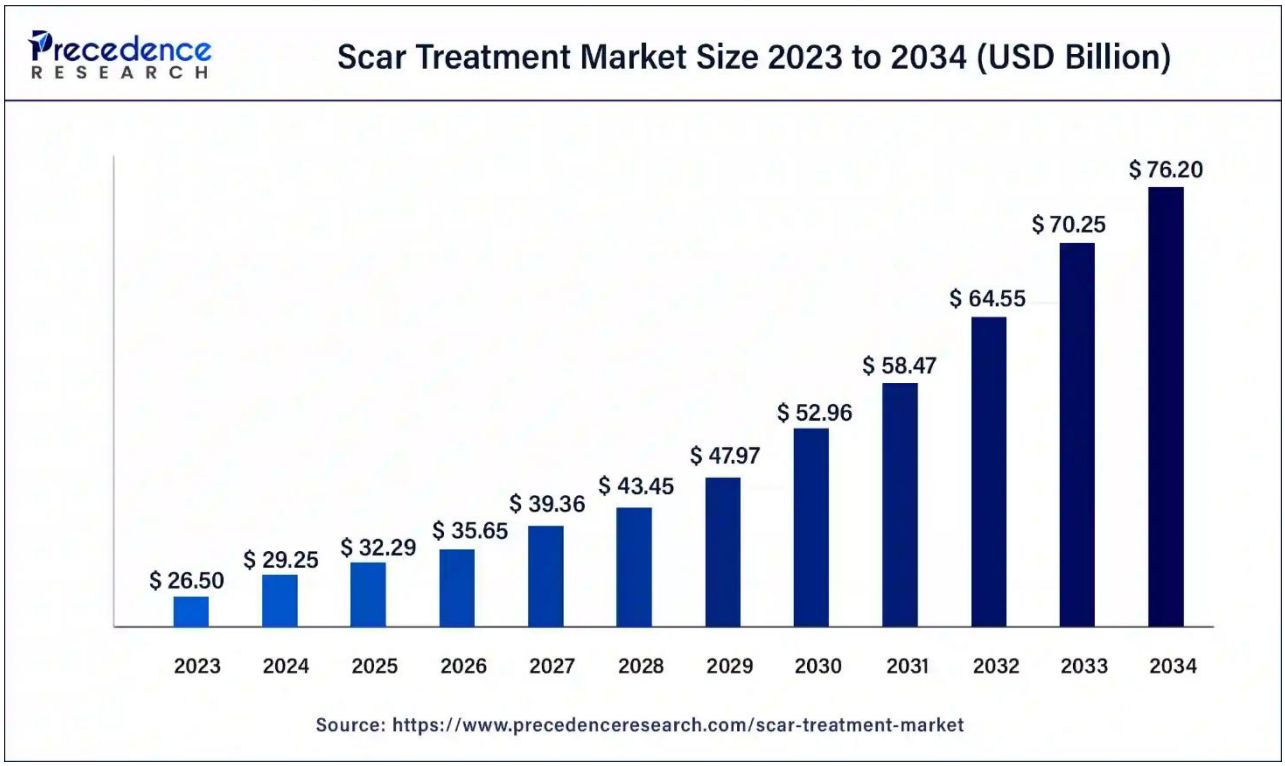

Figure 9: graph, sourced from Precedence Research, showing the projected growth of the global scar treatment market from $26.50 billion in 2023 to $76.20 billion by 2034, displaying a steady upward trend with accelerated growth after 2027.

The Asia-Pacific region is expected to experience the highest growth rate, with a CAGR of 12% between 2024 and 2034. Factors contributing to this growth include increased healthcare investments, a rising number of road accidents leading to scars, and growing awareness of aesthetic treatments.

The global scar treatment market is projected to grow from $26.50 billion in 2023 to $76.20 billion by 2034, driven by increasing aesthetic awareness and injury rates. With nearly half of people worldwide having scars and 100 million new cases annually, there's significant opportunity for innovative treatments like SNT-6302 & SNT-9465.

The prevalence of scarring is notable worldwide. An international study reported that nearly one in two individuals (48.5%) have at least one scar, with variations across countries: China (37%), Brazil (46%), the USA (53%), and Russia (61%). In the United Kingdom alone, over 20 million people are affected by skin scarring, with nearly a quarter experiencing short-term emotional or physical issues, and 14% enduring long-term physical or psychosocial disabilities. Annually, it is estimated that about 100 million people develop scars, with 11 million cases progressing to keloids.

Given the high prevalence and the limitations of current treatments, there is a substantial market opportunity for innovative therapies like SNT-6302. By targeting the underlying mechanisms of fibrosis through pan-lysyl oxidase inhibition, SNT-6302 has the potential to offer a more effective approach to both preventing and treating various types of scars, addressing a critical unmet need in dermatological care.

Skin Scarring Treatment

Traditional scar treatments primarily focus on symptom management rather than addressing the underlying causes of scar formation. Common approaches include

topical agents, laser therapies, surgical interventions, injectables, and regenerative medicine.

The market is segmented by treatment type, with topical agents holding a dominant share of 65.5%, equating to approximately USD 17.4 billion, based on available segmentation data from similar reports. The remaining market share is distributed among laser therapies (15%, USD 4 billion), injectables (10%, USD 2.65 billion), surgical interventions (5%, USD 1.325 billion), and regenerative medicine (4.5%, USD 1.1925 billion), estimated based on industry trends and comparative analysis.

Topical Agents

Silicone-based products are the gold standard for scar treatment, proven to reduce scar characteristics, while alternatives like onion extract show limited effectiveness. These affordable treatments require consistent use over months to deliver gradual results.

Topical therapies are the first-line, non-invasive approach for scar prevention and treatment. Silicone-based products are the most widely used and recommended topical scar treatments. These include silicone gel sheets and silicone gel ointments (e.g. Kelo-cote, Mepiform, BioCorneum which is silicone gel with SPF 30). Silicone creates an occlusive, hydration-balancing layer over the scar that can modulate collagen production. Clinical evidence supports the efficacy of silicone: a 2013 meta-analysis of randomized trials found that topical silicone gel significantly reduced scar pigmentation, height, and hardness compared to no treatment. Notably, silicone gel was as effective as silicone sheeting, and both outperformed many other topical remedies in improving post-operative scars. Silicone therapy is thus considered a gold standard for conservative scar management, especially for hypertrophic and keloid scars, with a generally safe profile.

Other popular topical agents include onion extract gels (e.g. Mederma, containing Allium cepa extract) and various vitamin or plant-based creams. Onion extract is widely marketed for scar reduction, but its evidence is mixed. Some small trials have reported slight improvements in scar softness or redness with onion extract, but overall it has not shown clear superiority over simple emollients. Vitamin E creams are commonly used by patients, but controlled studies have found no significant benefit and sometimes contact dermatitis; accordingly, there is little evidence that vitamin E helps scars.

In terms of cost, topical treatments are the most accessible: a month's supply of silicone gel or a reusable silicone sheet is on the order of tens of dollars, far cheaper than procedural therapies. The main drawback is that results are gradual and sometimes modest; patients must adhere to daily use for weeks to months. Still, given the minimal risk and evidence of benefit, silicone topicals are a cornerstone of scar management (often used in combination with other therapies).

Laser Therapies

Laser and light-based therapies have become mainstream for improving scar appearance and texture. Different laser modalities target various scar components—vascular lasers target redness, ablative lasers target scar thickness/texture, etc. Leading laser treatments include the pulsed dye laser (PDL) (e.g. Candela Vbeam) for red, raised scars and fractional ablative lasers (carbon dioxide CO_2 or erbium:YAG) for thick or pitted scars. Device manufacturers like Lumenis and Cynosure produce many of these systems. For example, Lumenis's UltraPulse CO_2 laser (with a deep FX and SCAAR FX mode) and Cynosure's Icon 1540 nm fractional laser are both widely used for scars. The Icon 1540 (a non-ablative fractional erbium glass laser) is notably the only FDA-approved non-ablative laser specifically indicated for treatment of surgical and acne scars, offering moderate improvement with little to no downtime. In contrast, the Lumenis UltraPulse CO_2 (ablative fractional) can achieve more dramatic remodelling of scar tissue, especially in severe scars, albeit with more healing time: its SCAAR FX™ mode penetrates deeply (up to ~4 mm) to treat thick scar bands.

For hypertrophic (raised) scars, the combination of a vascular laser and a fractional ablative laser is often considered best-in-class. Meanwhile, fractional CO_2 lasers are

regarded as the gold standard for improving scar texture – for example, softening the rigid collagen in burn scars or smoothing pitted acne scars.

Lasers can achieve improvements that topical agents cannot, by physically altering scar tissue. The other key advantage of lasers is that they can be combined with other therapies (e.g. laser plus steroid injections) for enhanced results. They can also treat large scar areas (e.g. a broad burn scar) in a session, which is harder to do with surgery. However, ablative lasers cause an open wound that takes ~1–2 weeks to heal. Laser treatment is also expensive, with each session costing a few hundred to over one thousand dollars, and multiple sessions (3-6) are typically required for optimal results.

Injectable Treatments

Injectables are mainly used for hypertrophic and keloid scars, treated with corticosteroids to reduce size and inflammation, and atrophic scars, where hyaluronic acid fillers improve appearance, also used to prevent scar formation or reduce visibility in specific cases. Leading options include corticosteroid injections (e.g., triamcinolone), hyaluronic acid fillers for atrophic scars, botulinum toxin to prevent scar formation, and enzymes like collagenase for keloid treatment. Studies show that corticosteroid injections can reduce the size of a scar by 50% or more, improving symptoms like itching and redness, with a meta-analysis revealing a significant improvement in Visual Analog Scale scores and Vancouver Scar Scale scores compared to controls. Injectable acne scar treatments can stimulate collagen production, offering immediate improvement in pitted scars, with minimal downtime. The market share is estimated at 10%, accounting for approximately USD 2.65 billion, driven by demand for minimally invasive solutions. Costs range from a few hundred dollars per session for corticosteroids to up to $1,500 per syringe for fillers. Advantages include minimally invasive administration and quick results, while disadvantages include the need for multiple sessions and potential side effects like skin thinning or discoloration.

Surgical Interventions

Surgical interventions are reserved for severe or disfiguring scars, including large or deep scars, functionally impairing scars, and those in cosmetically sensitive areas, typically considered when other treatments fail, addressing issues like contractures or significant aesthetic concerns. Common procedures include excision to remove scar tissue, skin grafting for large areas, Z-plasty and W-plasty for repositioning scars, dermabrasion for surface smoothing, and microneedling, though the latter may be considered minimally invasive. These are performed by plastic surgeons or dermatologists. Surgical interventions can improve the appearance and functionality of severe scars, but they carry risks such as infection, bleeding, and the possibility of new scar formation; for instance, a review found that while surgery can reduce scar appearance, recurrence rates are high, particularly for keloids, with no single modality proven superior. Costs can range from a few hundred to several thousand dollars, depending on complexity. Advantages include the ability to address complex or large scars, while disadvantages include invasiveness, higher risk of complications, longer recovery time, and higher cost.

Regenerative Medicine

Regenerative medicine targets severe or chronic scars unresponsive to other treatments, focusing on tissue regeneration, used for cases requiring advanced healing, such as post-burn scars or significant trauma, often in experimental or cutting-edge settings. Key therapies include platelet-rich plasma (PRP) to stimulate healing, stem cell therapy for tissue regeneration, and growth factor therapy to enhance collagen production. A notable example is Avita Medical's ReCell system, which uses a patient's own skin cells to create a spray for wound healing and reducing scarring in burn patients. ReCell is indicated for acute thermal burn wounds and may be used in other applications like vitiligo and repigmentation, with studies showing improved healing and reduced need for skin grafting. A randomized

controlled trial found ReCell to be effective in burn injuries compared to split-thickness skin grafts, with significant improvements in healing outcomes. Compared to topical agents, which are suited for milder, earlier-stage scars, ReCell is designed for severe injuries or burns, offering a more advanced, personalized treatment but at a higher cost and complexity. Stem cell therapy is still in the experimental phase with promising results: a systematic review found that regenerative medicine, including PRP, showed effectiveness in treating hypertrophic scars and keloids in all eight reviewed studies.

These therapies are promising but can be costly, with sessions ranging from $1,000 to $5,000, and may not be widely available. Advantages include using autologous cells to potentially reduce rejection risks and effectiveness for large areas, while disadvantages include high costs, the need for specialized equipment and training, and limited availability.

Category	Market Share (Approx.)	Estimated Market Size (USD Billion, 2023)	Cost Range (Per Treatment/Session)
Topical Agents	65.5%	17.4	$5 - $500
Laser Therapies	15%	4.0	$500 - $3,000+
Injectables	10%	2.65	$200 - $1,500+
Surgical Interventions	5%	1.325	$500 – Several Thousand
Regenerative Medicine	4.5%	1.1925	$1,000 - $5,000+

Figure 10: breakdown of the scar treatment market in 2023, categorizing treatment types by market share, estimated market size in USD billions, and cost ranges per treatment session.

Comparison to SNT-6302

SNT-6302 falls within the topical agent category, likely indicated for mild to moderate scars like acne or surgical scars, aligning with the category's focus. Its cost should be similar to other topical treatments, offering a cost-effective alternative compared to lasers, injectables, surgeries, or regenerative methods, enhancing accessibility for patients seeking non-invasive options. This positioning aligns with market trends toward accessible, at-home care options, making SNT-6302 a competitive choice in the skin scarring treatment market.

7. Valuation

We value Syntara at A$0.235 per share, representing 218% upside from the current A$0.074 share price. This valuation comes from our risk-adjusted net present value analysis of the SNT-5505 program, supported by industry M&A precedents, licensing comparables, and competitive landscape assessment.

M&A Precedents: Significant Upside for Syntara

Myelofibrosis

Recent M&A activity in the MF space highlights SNT-5505's significant potential. The 2023 acquisition of CTI BioPharma by Sobi for US$1.7 billion demonstrates big pharma's willingness to invest in novel treatments. CTI's pacritinib attracted interest after Phase III PERSIST-1 trial results showed 19.1% SVR in JAK2 inhibitor-naïve patients (versus 4.7% with best available therapy) and 46.1% reduction in TSS (versus 5.3%). Pacritinib's effectiveness in patients with Thrombocytopaenia—addressing a key unmet need in MF—drove this acquisition, setting a precedent for valuing innovative therapies like SNT-5505. Similarly, GSK's US$1.9 billion acquisition of momelotinib in 2022, following Phase III SIMPLIFY-1 results (26.5% SVR and 24.6% TSS reduction in JAK inhibitor-experienced patients), further demonstrates big pharma's interest in treatments with disease-modifying potential, aligning with Syntara's strategic focus.

M&A in MF Space

Drug	Target	Acquirer	Year	Upfront Payment	Further Payments	Drug Development Stage
Fedratinib	Impact Biomedicines	Celgene (acquired by BMS)	2018	$1.1B	Up to $1.25B	Phase III completed
Pelabresib	Constellation Pharma	MorphoSys	2021	$1.7B	N/A	Phase III ongoing
Momelotinib	Sierra Oncology	GSK	2022	$1.9B	N/A	Phase III completed
Bomedemstat	Imago BioSciences	Merck & Co.	2022	$1.35B	N/A	Phase II ongoing
Pacritinib	CTI BioPharma	Sobi	2023	$1.7B	N/A	FDA approved

Figure 11: Table summarizing recent M&A deals in the MF space, including drug targets, acquirers, deal values, and development stages

Myelodysplastic Syndrome

Merck's $11.5 billion acquisition of Acceleron Pharma in 2021 was driven by luspatercept's FDA approval for MDS-related anemia, where the MEDALIST trial showed 38% of transfusion-dependent patients achieving independence versus 13% with placebo. Similarly, Pfizer acquired Trillium Therapeutics for $2.26 billion in 2021 based on Phase 1b/2 results showing 30% of MDS patients achieving stable disease. Gilead's $4.9 billion acquisition of FortySeven in 2020 was motivated by Magrolimab's 42% response rate in higher-risk MDS patients when combined with azacitidine. SNT-5505 aligns with these high-value targets, suggesting that Syntara could attract similar attention if clinical trials, such as the ongoing Phase I/II studies, replicate or exceed these efficacy benchmarks.

M&A in MDS Space

Drug	Target	Acquirer	Year	Upfront Payment	Further Payments	Drug Development Stage
Alvocidib	Tolero Pharmaceuticals	Sumitomo Dainippon	2017	$200M	Up to $580M	Phase II (MDS preclinical)
Magrolimab	Forty Seven, Inc.	Gilead Sciences	2020	$4.9B	None	Phase 1b/2 (MDS trials planned)
TTI-621, TTI-622	Trillium Therapeutics	Pfizer	2021	$2.26B	None	Phase 1b/2 (Heme cancers, incl. MDS though not the primary focus)
Luspatercept (Reblozyl®)	Acceleron Pharma	Merck	2021	$11.5B	None	FDA-approved (MDS anemia)
ORM-6151	Orum Therapeutics (Program only)	BMS	2023	$100M	Up to $80M	IND cleared, Phase 1-ready (MDS/AML)

Figure 12: Table summarizing recent M&A deals in the myelodysplastic syndromes (MDS) space

Parkinson's Disease

Recent M&A in the PD treatment space too sets a compelling precedent for Syntara's overall value potential. Eli Lilly's 2020 acquisition of Prevail Therapeutics for $880 million upfront, with up to $160 million in milestone payments, was driven by PR001, a gene therapy for PD patients with GBA1 mutations, which demonstrated promising results in its Phase 1/2 PROPEL trial. Roche's 2020 acquisition of Inflazome for approximately US$400 million (CHF 380 million), with up to US$52.5 million (CHF 50 million) in milestones, focused on Inzomelid and Somalix, inflammasome inhibitors that completed Phase I trials, demonstrating safety in healthy volunteers with no dose-limiting toxicities and preclinical PD mouse model data showing a 40% reduction in neuron loss, a 25% increase in striatal dopamine levels, and improved motor performance on rotarod tests, directly linking NLRP3 inhibition to PD progression.

These deals, driven by promising clinical and pre-clinical data, set a precedent for substantial valuations, suggesting Syntara could see similar interest. Moreover, given that many of these deals were completed following promising early (phase I or II) clinical data, Syntara could see near to medium-term interest from big pharma if SNT-4728's ongoing Phase 2 trials yield similarly compelling efficacy and safety results.

M&A in PD Space

Drug	Target	Acquirer	Year	Upfront Payment	Further Payments	Drug Development Stage
PR001	Prevail Therapeutics	Eli Lilly	2020	$880M	Up to $160M	Phase I/II for PD
Inzomelid, Somalix	Inflazome	Roche	2020	$445M	Not specified	Phase I completed (inflammasome inhibitors relevant to PD)
PINK1 activator	Mitokinin	AbbVie	2023	$110M	Up to $545M	Pre-clinical (IND-enabling studies for PD)

Figure 13: Table summarizing recent M&A deals in the Parkinson's disease space, including the drugs, their targets, acquirers, deal values, and development stages

Licencing Agreements in MF & MDS: Setting a Precedent

Precedent licensing and partnership agreements in MF & MDS highlight the potential for SNT-5505 to attract strong interest from big pharma. This is highly pertinent to our valuation of Syntara as we predict the Company will strike a licensing deal upon completion of phase 3 results for SNT-5505 in MF.

Gilead Sciences' 2018 partnership with Sierra Oncology (now GSK) for momelotinib involved an upfront payment of US$3 million and milestone payments up to US$195 million, driven by Phase III SIMPLIFY-1 trial results, as previously mentioned in Section 4, showing a 26.5% SVR rate and a 24.6% TSS reduction in JAK inhibitor-experienced patients, alongside significant anaemia benefits.

Similarly, Incyte's 2009 agreement with Novartis for ruxolitinib, with an upfront payment of US$150 million and up to US$1.1 billion in milestones, was prompted by Phase III COMFORT-I/II trials, demonstrating a 41.9% SVR rate and 45.9% TSS reduction in MF patients compared to placebo, establishing a disease-modifying standard. These precedents illustrate that big pharma is willing to enter lucrative partnerships after strong Phase 2 or Phase 3 data, suggesting Syntara could secure a similar agreement for SNT-5505 if its full Phase 2 data is as robust as the interim data. Such an agreement would provide a critical funding injection, significantly accelerating SNT-5505's commercialization by offsetting development costs and expanding market reach, while also reducing Syntara's exposure to clinical risk compared to waiting for Phase 3 data. We expect, however, that Syntara will hold off signing a licensing deal until after completion of Phase 3 patient recruitment.

Partnership Agreements for MF Therapies

Drug	Company	Big Pharma	Year	Upfront Payment	Milestone Payments	Royalties	Development Stage
Ruxolitinib	Incyte	Novartis	2009	$150M	$60M + up to $1.1B	Mutual royalties: Incyte pays Novartis on US sales, Novartis pays Incyte on non-US sales (rates not specified)	In Phase III
Pacritinib	CTI (now Sobi)	Baxter	2013	$60M (including $30M equity)	up to $112M	Tiered royalties on ex-U.S. sales from Baxter to CTI (high single digits to mid teens)	In Phase III
Imetelstat	Geron	Janssen	2014	$35M	up to $900M	Tiered royalties on worldwide net sales (high single digits to mid teens)	In Phase II
Momelotinib	Gilead Sciences	Sierra (now GSK)	2018	$3M	up to $195M	Tiered royalties from mid-teens to high-twenties from GSK to Gilead on net sales	In Phase III

Figure 14: table detailing partnership agreements for MF therapies from 2009 to 2018, comparing four key drugs (Ruxolitinib, Pacritinib, Imetelstat, and Momelotinib) across multiple deal parameters.

Takeda's 2024 deal with Keros Therapeutics for elritercept, involving an upfront payment of US$200 million and up to US$1.1 billion in milestones, was spurred by Phase II trial data for elritercept (a TGF-β inhibitor), as previously highlighted in

Section 4, showing a 35% reduction in transfusion dependence in lower-risk MDS patients and a 28% improvement in haemoglobin levels compared to placebo. Likewise, Janssen's 2018 partnership with argenx for cusatuzumab, with a US$300 million cash and US$200 million equity upfront payment and up to US$1.3 billion in milestones, was driven by Phase I/II trial results, demonstrating a 42% overall response rate in higher-risk MDS patients when combined with azacitidine. These deals, often signed after promising Phase 2 data, suggest Syntara could negotiate a partnership for SNT-5505 following its full Phase 2 results.

Partnership Agreements for MDS Therapies

Drug	Company	Big Pharma	Year	Upfront Payment	Milestone Payments	Royalties	Development Stage
Elritercept	Keros Therapeutics	Takeda	2024	$200M	$1.1 billion	Tiered; global ex. China	Phase II
H3B-8800	Eisai	Roivant	2022	$8M cash; $7M equity	Not disclosed	Not disclosed; US & Europe	Preclinical
Rigosertib	Onconova Therapeutics	Knight Therapetuics	2019		CA$33.95M	Double-digit tiered; Canada	Phase III
Rigosertib	Onconova Therapeutics	Pint Pharma	2018	$2.5M	$42.75 million	Double-digit tiered; Latin America	Phase III
Cusatuzumab	argenx	Janssen	2018	$300M cash; $200M equity	Up to $1.3B	Double-digit sales royalties; Global	Phase I/II

Figure 15: Table summarizing partnership agreements for MDS therapies, including the drugs, partnering companies, deal structures, and development stages

Overall, the precedent of these licensing agreements, driven by robust clinical data from Phase 2 and beyond, indicates that Syntara could see substantial interest from big pharma for SNT-5505, especially if the promising interim Phase 2 results are sustained or improved in the full dataset and subsequent trials. Signing an agreement after Phase 2 would mitigate Syntara's exposure to clinical outcomes, while a post-Phase 3 deal could command higher valuations but carry greater near-term risk. Either strategy would position SNT-5505 for accelerated commercialization, leveraging big pharma's resources and expertise to transform Syntara's market potential in MDS, and MF.

SNT Licensing Agreement History

In 2015, Syntara (then Pharmaxis) entered into a significant licensing agreement with Boehringer Ingelheim, a leading global pharmaceutical company. This agreement centred around the Company's drug candidate PXS-4728A, an inhibitor targeting Semicarbazide-Sensitive Amine Oxidase/Vascular Adhesion Protein-1 (SSAO/VAP-1), with a primary focus on its potential application in treating Non-Alcoholic Steatohepatitis (NASH), a liver-related disease.

The deal was structured as an option and asset purchase agreement. Under the terms of the agreement, Boehringer Ingelheim acquired the rights to PXS-4728A, paying Syntara an upfront sum of €27.5 million (approximately A$39 million at the time). The agreement also included a series of potential milestone payments that could total up to A$750 million, contingent on achieving specific development, regulatory, and commercialization milestones.

This landmark deal highlighted Syntara's expertise in drug discovery, particularly in amine oxidase chemistry, and was seen as a validation of its research capabilities by partnering with a "big pharma" entity like Boehringer Ingelheim.

rNPV-derived Valuation

PoS Assumptions

MF and MDS blur the lines between haematology (the study of blood disorders) and oncology (the study of cancer) because they are malignancies originating in the

blood-forming tissues, among other reasons. In clinical practice, they are typically managed by haematologist-oncologists, specialists trained in both fields, due to their dual nature as blood disorders and cancers.

The tables below outline the probability of success (PoS) of drug development across various therapeutic areas and across phases of development. For our valuation model, we assume a PoS at the midpoint of oncology and all ex. oncology data in Orphan Drug development programs from phase I to approval (2.8% to 23.8%) – a figure of 13.3%. Note, Syntara received orphan drug designation from the FDA for SNT-5505 for the treatment of MF in 2020. This PoS factor is used 'risk adjust' the net present value of our forecasted net cash flows for SNT-5505 until the end of FY34.

Clinical PoS by Therapeutic Area					
Therapeutic Area	**PoS 1,2**	**PoS 2,3**	**Pos 3,App**	**PoS 1,APP**	**PoS 2,APP**
Oncology	57.6%	32.7%	35.5%	3.4%	6.7%
Metabolic/Endocrinology	76.2%	59.7%	51.6%	19.6%	24.1%
Cardiovascular	73.3%	65.7%	62.2%	25.5%	32.3%
CNS	73.2%	51.9%	51.1%	15.0%	19.5%
Autoimmune/Inflammation	69.8%	45.7%	63.7%	15.1%	21.2%
All ex. Oncology	73.0%	55.7%	63.6%	20.9%	27.3%

Figure 16: the probability of success rates across different therapeutic areas and development phases.

Clinical PoS by Therapeutic Area of Orphan Drug Development Programs					
Therapeutic Area	**PoS 1,2**	**PoS 2,3**	**Pos 3,App**	**PoS 1,APP**	**PoS 2,APP**
Oncology	72.0%	39.4%	14.4%	1.2%	2.8%
Metabolic/Endocrinology	84.3%	66.7%	77.8%	15.7%	31.1%
Cardiovascular	69.6%	77.6%	83.3%	21.7%	43.1%
CNS	85.0%	56.3%	32.0%	5.0%	8.3%
Autoimmune/Inflammation	76.3%	57.0%	31.3%	4.4%	8.8%
All ex. Oncology	81.5%	59.2%	66.3%	13.6%	23.8%

Figure 17: comparison success rates specifically for orphan drug development programs across therapeutic areas.

Development Strategy Assumptions

We anticipate Syntara's development strategy will focus on maximising the value of its pipeline assets while efficiently managing resources and risk. We expect the Company to complete its Phase 2 trials of SNT-5505 in MF before advancing to a pivotal Phase 3 trial. Upon successful completion of the Phase 3 trial and the generation of positive topline data, we suggest Syntara will aim to secure a global licensing deal with a major pharmaceutical partner. This partnership will see the partner oversee regulatory submissions, commercialisation, and market expansion, ensuring broad patient access. We expect the licensing deal to be structured with an upfront payment of US$150 million (to reflect the de-risking of the asset by Syntara), milestone payments of up to US$400 million, and ongoing tiered royalties on net sales, assumed at a base of 10%. We propose the milestone payments schedule will be executed as follows:

- US$50m upon FDA acceptance of New Drug Application (NDA) filing
- US$250m upon FDA approval
- US$50m for first commercial sale, marking the start of revenue generation
- Further sales-based milestones of US$50m in aggregate

To maintain strategic focus, we anticipate the Company will pursue out-licensing agreements for SNT-4728 and SNT-6302 upon completion of their respective Phase 2 trials. This approach would allow the company to concentrate its resources on the more clinically advanced SNT-5505 program while leveraging external partners to drive the development and commercialisation of its other assets. Due to the SNT-4728 and SNT-6302 programs not yet having performance data, we refrain from incorporating cash flows from potential licensing deals for these assets.

Phase 3 Timeline & Development Cost Assumptions

We anticipate that the pivotal Phase 3 clinical trial for SNT-5505 in MF will require significant investment and take approximately three years from first patient enrolment to primary completion, with additional time required for data analysis and regulatory submission. The timeline will be driven by several key phases, beginning with trial initiation and regulatory approvals, which can take between six to twelve months. This stage includes securing approvals from agencies such as the FDA and other global regulators, selecting trial sites, negotiating contracts, and obtaining ethics committee clearances. The next phase, patient recruitment, is expected to take between twelve to twenty-four months. Recruitment can be a major bottleneck, particularly in an orphan disease such as MF. Similar trials, such as the MOMENTUM phase 3 trial of momelotinib conducted by Sierra Oncology, took approximately eighteen to twenty-four months to fully enrol 195 patients across twenty-one countries. Based on precedent studies, we estimate that SNT-5505's recruitment phase will take one and a half to two years, depending on the trial design and site selection strategy.

Following recruitment, the treatment and follow-up phase will take between six to twelve months to complete its primary endpoint assessment. MF trials typically evaluate symptom reduction and spleen volume response at twenty-four weeks, a standard regulatory endpoint for therapies in this space. While primary analysis will be conducted within this timeframe, extended follow-up may be required for long-term efficacy and safety monitoring. Once the treatment period concludes, the final stage of the trial, which includes data analysis and regulatory submission, is projected to take an additional six to twelve months. The process of database lock, statistical analysis, preparation of the clinical study report, and regulatory submission is essential for ensuring the trial meets all compliance and efficacy requirements. Given these factors, we forecast a total trial duration of between two and a half to four years, with three years as a reasonable baseline.

The expected cost of the Phase 3 trial is estimated to range between A$50 million and A$80 million (US$30–50 million), aligning with industry norms for haematology and oncology trials of a similar scale. To be conservative, our model uses a total cost of US$50 million. Given that myelofibrosis is an orphan disease and requires complex assessments, such as spleen imaging and transfusion tracking, the per-patient costs may be higher than seen in other disease areas. We anticipate the trial will enrol approximately 250 patients.

Included in the total cost of the trial, a Phase 3 trial budget typically allocates 20-30% (A$15-25M) to CRO services for essential activities like site monitoring and data management. Regulatory compliance requires 10-15% (A$5-10M) for ethics approvals and pharmacovigilance, while drug manufacturing and logistics demand 5-10% (A$5-7M) to support the large-scale patient enrolment characteristic of Phase 3 studies.

The overall cost of the trial will also be influenced by regional variations. Clinical trials conducted in the United States are typically the most expensive, with per-patient costs often thirty to fifty percent higher than in regions such as Australia or Eastern Europe. Conducting a portion of the trial in Australia is particularly attractive due to the country's R&D Tax Incentive.

What	When
Phase 2 final data	H2 2025
FDA EOP2 Meeting	Mid-2025
Phase 3 start	Early 2026
Phase 3 Completion	Early 2029
NDA Filing	Late 2029 – Early 2030
FDA Approval	Mid – Late 2030

Figure 18: our forecast for SNT-5505 development timeline for MF. The table presents the key milestones and expected completion dates.

Approval, Market Penetration & Revenue Assumptions - MF

Continuing on from our assumption that Syntara strikes a licensing deal on the back of Phase 3 completion, the partner is likely to file an NDA for SNT-5505 in late 2029 to early-2030 under a standard timeline, assuming a full Phase 3 trial post-2025. However, an accelerated path could see a filing as early as late 2026 to mid-2027 if Phase 2 data supports it and the FDA agrees to a faster track. The most probable window, balancing optimism and realism, hinges on the 2H 2025 data and FDA discussions, with 2029-2030 being a conservative yet plausible date.

In forecasting market penetration for SNT-5505 in the treatment of MF, we have adopted a conservative approach, reflecting the competitive landscape and historical trends of new drug adoption in rare haematologic and oncologic diseases. For the US, we assume penetration starts at 5% in FY31 (the first year of sales post mid-2030 FDA approval), increasing to 10% in FY32, 15% in FY33, and reaching 20% by FY34. For global markets, we project a slower uptake due to regional healthcare disparities, starting at 3% in FY31, rising to 6% in FY32, 9% in FY33, and 12% by FY34. These rates are informed by the market entry of ruxolitinib, which, despite being a first-in-class JAK1/JAK2 inhibitor, achieved a 40% compound annual growth rate in sales from 2012 to 2022, ultimately capturing a 70% market share of treated MF patients in the USA by 2022 (approximately 16,067 patients out of 20,000). However, as a later entrant and given its use as an adjunct therapy to ruxolitinib, SNT-5505 faces a more established market, justifying our gradual penetration assumptions, which balance the potential to capture patients with suboptimal ruxolitinib responses (30-50% of cases) against the challenges of displacing an entrenched standard of care.

We project SNT-5505 will be priced SNT-5505 at US$100,000 annually for MF patients in the United States, consistent with the premium pricing established in this therapeutic area. Real-world data and patient assistance programs indicate ruxolitinib's annual cost exceeds $100,000, while fedratinib commands approximately $90,000-$100,000 per year. Pacritinib, which targets cytopenic MF patients, and momelotinib, approved in 2023 with distinct anemia benefits, maintain premium pricing between $80,000-$110,000, reflecting their specialized applications and limited competition.

For markets outside the United States, we anticipate an average annual price of US$50,000 for SNT-5505, reflecting the established pricing patterns of comparable therapies. Ruxolitinib is typically priced lower internationally due to negotiated healthcare frameworks. The American Journal of Managed Care cites the cost in certain European countries:

- UK: £44,905 (in 2013; 70,262 USD)
- Portugal: €40,000 (in 2016; 44,272 USD)
- Chile: US$54,500 (in 2016)
- Canada: CA$61,444 (in 2012; 61,474 USD)
- Finland: €42,367 (in 2015; 42,027 USD)

Fedratinib, approved in 2019, follows similar international pricing trends at approximately US$50,000 in Europe, reflecting its second-line positioning. Pacritinib, primarily available in the US since its 2022 approval, shows limited global presence but maintains pricing comparable to ruxolitinib where available. Momelotinib, with its 2023 approval and EMA authorization, commands US$45,000-US$55,000 annually.

The proposed US$50,000 global price point for SNT-5505 strategically balances these benchmarks while accounting for regional purchasing power variations, reimbursement structures, and development cost recovery needs, while remaining competitive within the established US$40,000-$60,000 range for JAK inhibitors in high-income markets outside the US.

Approval, Market Penetration & Revenue Assumptions - MDS

Following on from the assumptions applied to SNT-5505 in MF, we adopt a similarly conservative approach to forecasting approval and market entry for the drug's entry into the MDS market. In MDS, the drug faces a relatively complex treatment paradigm, characterized by a broader variety of patient subtypes, a competitive landscape with multiple emerging therapies, and historically cautious adoption of new treatments.

We forecast that the Company will complete a full phase 3 trial post-FY29, with filing of an NDA in FY31. Allowing time for data review and standard regulatory process, we expect FDA approval in early to mid-FY32. As for ex-US markets, we assume registration efforts in key jurisdictions such as Europe, Japan, and select Asia-Pacific countries will culminate in product launch in FY33.

Upon receiving approval in the US, we anticipate sales will start in late FY32, with initial adoption slower compared to MF. In FY32, we expect 1.5% penetration of the addressable US MDS population, rising gradually to 6% in FY34, reflecting both the caution in newer MDS therapies and the complexities of segmenting patients between monotherapy (low-risk) and combination approaches (higher-risk). Market education, specialist endorsements, and real-world evidence will be the key drivers of gradual uptick. For the ex-US rollout, we adopt a conservative stance on market share gains, starting at 1% in FY33 – coinciding with first approvals in Europe and other major regions – and reaching 4% by FY35. Varied reimbursement frameworks will likely elongate adoption curves, consistent with slower MDS drug uptake historically seen outside the US.

We assume a global ex-US average annual cost of US$50,000 per patient for SNT-5505 in MDS. This figure aligns with pricing benchmarks for high-value, specialist haematology treatments in ex-US regions and remains comfortably within the established US$40,000-US$60,000 range for emerging therapies in high-income markets.

While incidence of MDS is projected to decline annually hereon (as reported in a study featured in Frontiers in Oncology – "Global, regional, and national burden of myelodysplastic syndromes and myeloproliferative neoplasms, 1990-2021: an analysis from the global burden of disease study 2021"), the overall prevalence of MDS is expected to rise. Sources on the internet provide wide-ranging prevalence estimates, with Orphanet, for example, estimating global prevalence of MDS at between 1 and 9 per 100,000 people.

Risked-NPV

To value the SNT-5505 development program, we apply a WACC of ~14.6% to discount forecasted future net cash flows, including associated corporate operational costs. Our WACC calculation incorporates a Beta of 1.33 (calculated from one year of historical returns), a risk-free rate of 4.1%, and a cost of equity of 12%. The capital structure assumes 100% equity funding.

This approach yields a present value (PV) of approximately A$597.52 million for the projected cash flows. For the terminal value calculation, we apply a long-term growth rate of 4%, which balances our cautious sales projections while considering potential upside from drug sales that only commence late in our forecast period. The resulting PV of the terminal value is approximately A$2.3 billion.

Combining these components, we estimate the total net present value (NPV) of the SNT-5505 program at approximately A$2.9 billion. After applying the probability of success (PoS) factor detailed earlier in this report's Valuation section of 13.3%, we arrive at a risk-adjusted NPV (rNPV) of A$381.3 million for the SNT-5505 development program.

Risk-Adjusted NPV (rNPV)	
Sum of PVs	597.52
Long term growth rate (g)	4%
FY34 Net Cash Flow * (1+g)	934.80
Terminal Value (TV)	8,843.61
PV of (TV)	2,269.37
NPV of Program	**2,866.89**
PoS	13.3%
rNPV	**A$381.30m**

Table 3: rNPV calculation table

Syntara Valuation

We determine a fair value of A$0.235 per share for Syntara. Our approach focuses exclusively on Syntara's flagship program, SNT-5505, for MF and MDS, yielding an equity value of A$381.3 million. We have deliberately excluded Syntara's earlier-stage pipeline assets in skin scarring and Parkinson's disease from our valuation model, as these programs have yet to generate meaningful performance data. This conservative stance reflects our expectation that Syntara will likely license out these drug development programs following successful Phase 2 clinical trials, making it premature to forecast the specific terms and financial impacts of such licensing agreements. Our current valuation intentionally understates Syntara's potential, highlighting significant upside beyond the flagship program once the earlier-stage pipeline assets progress and demonstrate clinical validation.

Valuation	
Net Debt	-17.91
Enterprise Value	363.39
Equity Value	381.30
Shares Outstanding (millions)	1,623.33
Fair Valuation	**A$0.235**

Table 4: fair valuation per share calculation

Downside Scenarios

The ultimate downside scenario occurs should phase 2 topline data for SNT-5505 in MF doesn't meet primary and/or secondary endpoints, suggesting insufficient efficacy to warrant further clinical development. In this scenario, Evolution anticipates a highly negative market reaction.

Secondly, should the company not pursue further clinical development of SNT-5505 in MDS, we estimate the fair valuation of Syntara ordinary shares is A$0.135. This valuation reflects the complete removal of further development costs beyond that required for phase 2 as well as removal of all revenues associated with MDS prescriptions of SNT-5505. As our model already incorporates a 13.3% probability of success factor (probability that an asset moves from phase 1 to regulatory approval), we assert that this scenario presents as a downside case rather than a base case, therefore not factoring into our fair valuation estimate.

Additional Share Issue

To execute on their strategy of developing SNT-5505 through a phase 3 clinical trial, Syntara must raise additional capital. Referring to figure 15 in the appendix, Evolution anticipates Syntara will raise further capital in FY26 and FY27. We expect the company will raise A$30 million at a 25% premium to the current share price - $0.10 (resulting in the issue of 300 million ordinary shares). This is because we anticipate re-rating of the stock on the back of positive expected phase 2 clinical trial results for SNT-5505 in MF. To progress the phase 3 throughout the duration of the trial, we expect the Company to complete further capital raising in FY27 – A$40 million at $0.12 per share (resulting in the issue of 333.33 million shares). Our price increase here

is founded on the expectation of positive results in other areas of the pipeline as well as unhindered operation of the phase 3 in MF. At the end of FY27, we suggest the total of ordinary shares outstanding equals 2,256,661,138.

8. Key Risks

Clinical Development Risk

Syntara's lead candidate, SNT-5505, and other pipeline assets remain in various stages of clinical development. The success of these programs depends on positive outcomes in ongoing and future clinical trials. Key risks include efficacy and safety concerns, as future trials may not confirm the promising early-stage data for SNT-5505. Unexpected safety issues or suboptimal efficacy could delay or terminate development. The process of obtaining regulatory approval is uncertain and subject to stringent requirements from agencies such as the FDA and TGA. Even with positive trial results, regulatory hurdles could delay market entry. Clinical trials are expensive and time-consuming. Delays in patient recruitment, trial design issues, or unforeseen adverse events could hinder the progress of Syntara's pipeline.

Competitive Landscape

Syntara operates in a highly competitive environment, particularly in the myelofibrosis and broader haematology/oncology spaces. The presence of existing market leaders, such as JAK inhibitors like ruxolitinib and newer entrants like fedratinib, pacritinib, and momelotinib, poses a challenge. SNT-5505 will need to demonstrate superior efficacy or safety to capture market share. Other companies are actively developing novel therapies for myelofibrosis and related conditions. Competitive advancements could diminish Syntara's commercial opportunity if superior treatments emerge before SNT-5505 gains approval. Even with regulatory approval, gaining traction in the market will require substantial commercial efforts, including physician education, reimbursement approvals, and effective sales strategies.

Funding Risk

As a clinical-stage biotech company, Syntara relies on external funding to advance its pipeline. The company will require additional funding to complete late-stage trials and support commercialization efforts. While the recent $15M capital raise extends runway to mid-2026, further funding will likely be needed. Additional capital raises could lead to shareholder dilution if new equity is issued at a discount. The biotech sector is highly sensitive to market sentiment. Negative clinical trial results, macroeconomic conditions, or shifts in investor appetite for speculative stocks could impact Syntara's ability to raise capital on favorable terms.

Commercialisation & Market Access

Even if SNT-5505 and other assets successfully complete clinical development, challenges remain in bringing them to market. Securing reimbursement agreements with government and private payers is crucial for commercial success. Pricing pressures or unfavorable reimbursement terms could limit market adoption. Syntara may seek strategic partnerships for commercialization. The ability to secure favorable deals depends on clinical data strength and market conditions. Scaling up production to meet commercial demand introduces operational risks, including supply chain disruptions and quality control challenges.

IP & Legal

Syntara's ability to protect its proprietary technology and assets is essential for maintaining competitive advantage. While Syntara holds patents covering its lead assets, challenges from competitors, generic entrants, or patent litigation could erode exclusivity. Changes in regulatory policies, patent disputes, or unexpected legal hurdles could impact the commercialization pathway

Macroeconomic & Sector-Specific Risks

External factors could also influence Syntara's trajectory, including economic conditions, market downturns, inflationary pressures, and interest rate fluctuations that could impact investor sentiment and funding availability. The biotechnology sector is subject to rapid shifts in investor confidence, driven by clinical trial outcomes, regulatory changes, and broader healthcare trends. Global supply chain disruptions, international trade tensions, or regulatory changes in key markets could introduce additional uncertainties.

9. Appendix

i. Financial Statements

Income Statement					
A$'000s	FY23a	FY24a	FY25e	FY26e	FY27e
Revenue	-	-	-	-	-
Other Income	6.35	5.85	5.63	11.79	14.76
Total Revenue	**6.35**	**5.85**	**5.63**	**11.79**	**14.76**
Operating expenses	-17.71	-18.90	-18.17	-38.07	-47.67
EBITDA	-11.36	-13.05	-12.54	-26.28	-32.91
D&A	-1.85	-0.23	-	-	-
EBIT	-13.21	-13.28	-12.54	-26.28	-32.91
Net Interest	-0.22	-0.39	-	-	-
NPBT	-13.43	-13.67	-12.54	-26.28	-32.91
Tax expense	-	-	-	-	-
NPAT (discontinued operations)	2.07	-1.48	-	-	-
NPAT	-11.36	-15.14	-12.54	-26.28	-32.91

Balance Sheet					
A$'000s	FY23a	FY24a	FY25e	FY26e	FY27e
Cash	9.23	3.52	9.47	11.37	16.91
Receivables	7.81	6.25	5.00	8.00	7.95
Other	1.64	-	0.50	1.75	2.80
Current assets	18.68	9.77	14.97	21.12	27.66
Receivables	2.82	0.06	0.50	2.28	3.00
PPE	1.84	0.38	0.30	0.30	0.39
Intangible assets and Other	0.68	0.17	0.54	0.91	1.20
Non-current assets	5.35	0.61	1.34	3.49	4.59
Total assets	24.03	10.38	16.31	24.61	32.25
Trade and other payables	4.72	4.32	4.18	8.76	9.30
Borrowings	2.04	0.16	-	-	-
Other	1.27	0.98	-	-	-
Current liabilities	8.03	5.45	4.18	8.76	9.30
Borrowings	6.32	0.08	-	-	-
Other liability	0.12	0.17	-	-	-
Non current liabilities	6.43	0.25	-	-	-
Total Liabilities	14.47	5.70	4.18	8.76	9.30
Net Assets	9.56	4.68	12.14	15.85	22.95
Contributed Equity	389.70	399.32	419.32	449.32	489.32
Retained earnings	-404.45	-419.60	-432.14	-458.42	-491.33
Reserves/Other	24.31	24.95	24.95	24.95	24.95
Total equity	9.56	4.68	12.14	15.85	22.95

Statement of Cashflows					
A$'000s	FY23a	FY24a	FY25e	FY26e	FY27e
Net profit for period	-11.36	-15.14	-12.54	-26.28	-32.91
Depreciation & Amortisation	1.85	0.23	-	-	-
Changes in working capital	-	-0.61	0.52	-0.33	0.46
Other	-	0.26	-	-	-
Operating cash flow	-9.51	-15.26	-12.03	-26.61	-32.45
Payments for PPE	-0.14	-0.01	-	-	-
Acquisition payments	-	-	-	-	-
Proceeds from asset sale	0.01	1.49	-	-	-
Investing cash flow	-0.13	1.49	-	-	-
Equity Raised	10.00	10.00	20.00	30.00	40.00
Transaction costs	-0.74	-0.68	-1.00	-1.50	-2.00
Lease liability payments	-2.25	-2.11	-0.24	-	-
Borrowings	-	-	-	-	-
Other	-0.03	-0.02	-	-	-
Financing cash flow	6.98	7.20	18.76	28.50	38.00
Free cash flow	**-9.64**	**-13.78**	**-12.03**	**-26.61**	**-32.45**
Cash flows	**-2.66**	**-6.58**	**6.73**	**1.89**	**5.55**
Effects of exchange rate	0.72	0.09	-	-	-
Cash year end	9.23	2.74	9.47	11.37	16.91

Investment Fundamentals					
	FY23a	FY24a	FY25e	FY26e	FY27e
Liquidity					
Quick Ratio	1.2	1.1	1.3	1.1	1.2
Solvency					
Debt to Equity	0.9	0.1	0.0	0.0	0.0
Debt to Assets	0.3	0.0	0.0	0.0	0.0
LT Debt to Assets	0.3	0.0	0.0	0.0	0.0
Profitability					
Net Margin	n/a	n/a	n/a	n/a	n/a
ROA	-47%	-88%	-94%	-128%	-116%
ROE	-119%	-213%	-149%	-188%	-170%
Valuation					
P/E	n/a	n/a	n/a	n/a	n/a
EV/EBITDA	n/a	n/a	n/a	n/a	n/a
P/B	3.69	6.12	10.70	9.71	7.87

Figure 19: sourced from company data and Evolution Capital forecasts

ii. Board & Management

Name	Position	Bio
Dr. Kathleen Metters	Chair (Non-Executive)	Appointed Chair in October 2023 after joining the board in 2020. With over 30 years in pharmaceuticals, she held senior roles at Merck & Co., including VP of External Basic Research, and was CEO of Lycera Corp. She brings expertise in drug development and strategic leadership to Syntara's oncology focus. Holds a PhD in Pharmacology from Imperial College London.
Gary Phillips	Chief Executive Officer (CEO)	CEO since March 2013, with over 30 years in pharmaceuticals, including leadership at Novartis. He led Syntara's pivot to blood cancer therapies like SNT-5505. Holds a B.Pharm and MBA, and is a Non-Executive Director at Arovella Therapeutics.

Tim Luscombe	Chief Financial Officer (CFO)	10 years of finance and commercial experience working with public and private companies in Australia and abroad. Currently serving as CFO and company secretary for several ASX-listed, pubic unlisted and private companies.
Kristen Morgan	General Manager, Drug Development	Joined in 2007, appointed General Manager in October 2023. With a PhD in Immunology, she oversees clinical development, notably myelofibrosis trials, drawing on 15+ years in biotech regulatory and scientific roles.
Wolfgang Jarolimek	Head of Drug Discovery	Joined in 2002, leads drug discovery with a PhD in Pharmacology. He drives Syntara's amine oxidase platform, developing SNT-5505 and SNT-4728, with prior experience at GlaxoSmithKline.
Jana Baskar	Chief Medical Officer	20+ years' experiences both in clinical medicine and the biopharmaceutical industry. Fomer medical director at Novartis Oncology in Australia and former medical director for IQVIA in Australia and New Zealand.
Simon Green	Non-Executive Director	Joined in December 2022. With 30 years in pharmaceuticals at Merck and Novartis, including as CEO of Merck Australia, he offers strategic and commercial guidance to the board.
Hashan De Silva	Non-Executive Director	Appointed in January 2023. An experienced life sciences investor, he was Head of Healthcare Research at Karst Peak Capital until December 2022 and founded KP Rx. With a Bachelor's in Medicine and Master's in Finance from UNSW, and as a CFA, he brings biotech and financial expertise. Also a Non-Executive Director at CurveBeam AI.

iii. Company History

Founding and Early Development

- 1998: Syntara was founded as Pharmaxis by Brett Charlton and William Cowden, focusing initially on pharmaceutical research for chronic respiratory and autoimmune diseases. This marked the beginning of its journey in drug development, leveraging expertise in amine oxidase chemistry.

- 2003: Pharmaxis was listed on the Australian Securities Exchange (ASX) with the code PXS on November 10, 2003, enabling access to capital markets for further research and development.

Respiratory Product Milestones

- 2011, May: Aridol, a lung function test for asthma diagnosis, received FDA approval for the US market, marking a significant achievement in respiratory diagnostics. This approval facilitated commercial sales, enhancing the company's global presence.

- 2012, April: Bronchitol, a treatment for cystic fibrosis, was approved in the European Union, expanding its market reach. This approval was crucial, with initial sales expected by June 2012, particularly in Germany and the UK, representing 40% of the European market by value.

- 2013: Due to corporate restructuring, Aridol sales were discontinued in the US, reflecting a strategic shift to streamline operations and focus on more promising areas.

- 2018, August: Aridol was relaunched in the US following FDA approval for the Sydney manufacturing facility, resuming sales through exclusive distributor Methapharm Inc. This relaunch was significant, demonstrating resilience in overcoming previous market challenges.

- 2020, October: Bronchitol received FDA approval for the US market, a transformational milestone for Pharmaxis, enabling sales as an add-on therapy for cystic fibrosis patients aged 18 and older. This approval was accompanied by milestone payments from partner Chiesi Farmaceutici SpA, strengthening financial stability.

Shift to Blood-Related Cancers

- 2020, July: PXS-5505, the lead drug candidate for blood-related cancers, was granted orphan drug designation by the FDA for myelofibrosis, qualifying for development incentives like reduced regulatory fees and extended market

exclusivity. This designation underscored its potential in addressing high unmet needs in myelofibrosis treatment.

- 2021, February: The first patient was enrolled in a phase 1c/2a clinical trial for PXS-5505, targeting myelofibrosis patients intolerant, unresponsive, or ineligible for JAK inhibitor drugs. This trial, cleared under the FDA's Investigational New Drug scheme, commenced with sites in Australia, South Korea, and later the US, focusing on safety and efficacy.

- 2023, July: Positive interim data from the phase 2 study of PXS-5505 in myelofibrosis were announced, showing promising tolerability and clinical efficacy, presented at the American Society of Haematology annual meeting. This data reinforced the drug's potential as a breakthrough therapy.

- 2024, December: Another set of positive interim data from the ongoing phase 2 study of SNT-5505 (formerly PXS-5505) in combination with ruxolitinib for myelofibrosis was announced, presented at the 66th American Society of Haematology annual meeting, suggesting excellent tolerability and improvements in symptoms and spleen volume.

Rebranding And Strategic Focus

- 2023, October: Pharmaxis underwent a major restructure, rebranding to Syntara Limited, and sold its mannitol respiratory business (including Aridol and Bronchitol) to Arna Pharma Pty Ltd on October 18, 2023. This sale, with residual net exit costs under A$1m and ongoing royalties, reduced core expenses by over 60%, saving over A$14m annually. The rebranding, approved by shareholders and registered by ASIC, saw the ASX code change from PXS to SNT on December 4, 2023, focusing primarily on clinical development for haematological malignancies.

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