ESN CLEER

Developing novel therapeutics for orphan indications in Cardiovascular Disease

Total Addressable Market & Commercialisation

- IPO
- Licensing
- Mergers & Acquisitions
- Royalty Financing

"***The lifeblood of our industry***", Roel van den Akker, PwC partner and pharmaceutical and life sciences deals leader,

Fierce Biotech, Jan 2024

Video: Why ESNtx005 is highly attractive to Pharmaceutical companies to fulfill the industry gap.

August 2024 update

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Executive Summary

ESN Cleer is developing its repurposed drug addressing specific segments of Cardiomyopathy diseases with clinical unmet needs. Here, we present a concise overview of ESN Cleer's (1) the total addressable market, (2) key stakeholders involved, and (3) the well-established commercialisation pathway within the industry.

(1) ESN Cleer's Total Addressable Market:

Patient Population

- Currently, ESN Cleer's total addressable market consists of two specific lead indications with <200,000 and <100,000 patient populations respectively.
- Collectively, ESN Cleer's drug sales are projected to reach US$ 6 billion within 6 years from FDA approval.

(2) Key Stakeholders:

Pharmaceutical Companies

- Substantial incentives from the US government's *1983 Orphan Drug Act* to develop orphan drugs.
- Between 2017-21, FDA approved 242 new drugs marketed in the US, 118 (48.8%) were orphan drugs.
- Orphan drugs are at CAGR 12%, projected to reach US$300 billion in sales and reach 20% of all drug sales by 2028.

Payer

- The high cost of Orphan drugs is ultimately "paid for" by either or both, Medicare and Medicaid government programs.
- In 2021, the US government spent US$ 92 billion (>30% of all drugs) on orphan drugs with its Medicare and Medicaid programs.

(3) Commercialisation:

ESN Cleer is positioned to access the aforementioned addressable market and key stakeholders through its (a) out-licensing model and (a) Mergers & Acquisition opportunities. These approaches offer the company effective means to capitalize on its developments and expand its presence within the market.

(a) Out-licensing Model

- Prevalent operational model commonly adopted within the industry.
- Royalty-based, continuous revenue business model, effective leverage of established and efficient supply-chain.
- ESN Cleer maintains its core strategy in innovation and development of orphan drugs for rare diseases.

(b) Mergers & Acquisitions

- Efficient resource deployment to attain optimal results.
- Significant value-growth for all stakeholders.

ESN Cleer is entering a US$ 300 billion rare diseases – orphan drugs market with industry-proven commercialisation pathway.

Aug '24 update

ESNtx005 is well-positioned to support the greatest challenges of the pharmaceutical industry in recent times

1. Introduction

ESN Cleer represents a pioneering biotechnology company dedicated to revolutionizing the approach to tackling Cardiomyopathy. The central focus revolves around the repurposing of extensively studied molecules for previously unexplored yet critically important medical applications. ESN Cleer specializes in repurposing drugs designed for orphan indications, addressing rare diseases that lack specific pharmaceutical interventions. These efforts are aimed at addressing some of the primary causes of Heart Failure, a condition that significantly impacts a broad spectrum of individuals within the Cardiovascular Disease (CVD) population. Such diseases and syndromes not only carry a substantial risk of mortality but also have a profound detrimental effect on the quality of life for those affected, underscoring the profound significance of ESN Cleer's mission.

Navigating the pharmaceutical industry is a complex endeavor, encompassing the entire spectrum from drug development to ensuring patient access. Traditionally, major pharmaceutical corporations invest substantial financial resources, often spanning decades, to research, develop, and introduce entirely new "blockbuster" drugs to the market. Frequently, these drugs become the standard for treating prevalent diseases among the general population. However, this focus has resulted in a gap within the realm of rare diseases, where specific ailments with critical unmet needs persist (*See Fig 1.1*).

The passage of the Orphan Drug Act of 1983 by the US Congress incentivized pharmaceutical companies to concentrate on developing treatments for populations afflicted by rare diseases (defined as affecting fewer than 200,000 patients). Orphan drugs typically command higher price points due to the elevated expenses associated with their development, manufacturing, and marketing. To facilitate access to these often costly medications for rare disease patients, subsidies are made available through government programs such as Medicare and Medicaid.

ESN Cleer has achieved the reformulation of its drug to achieve a high level of purity and stability, with each impurity reduced to a fraction of its original amount. The company is currently in its pre-clinical phase and is strategically positioned to enter market segments that align with both the industry and receive support from the US government and regulatory bodies (*See Table 3.1*).

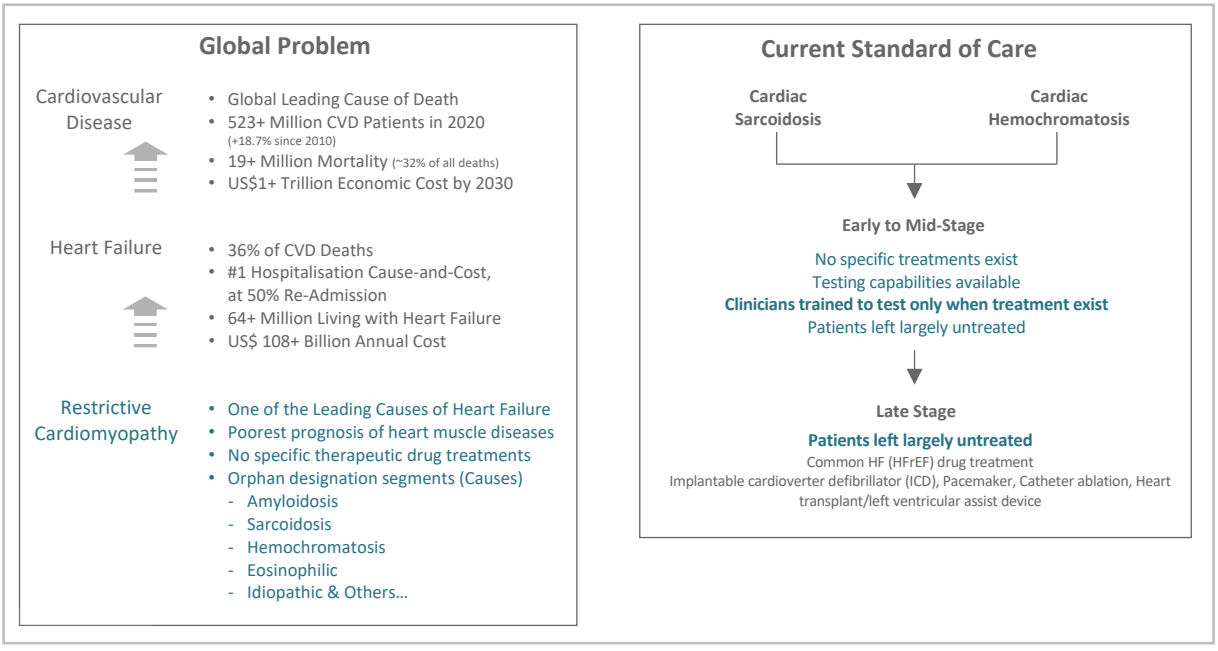


Fig 1.1 ESN Cleer's strategy to develop novel therapeutics for orphan indications in Cardiomyopathy

2. Total Addressable Market

Patient Population

ESN Cleer centers its attention on addressing specific orphan indication segments within the Cardiomyopathy market. These targeted conditions encompass populations of less than 200,000 and 100,000 new patients per year, respectively, within the United States.

Most recent new cardiovascular drug with orphan designation

In April 2022, the FDA granted approval for the novel drug Camzyos (Mavacamten) with an orphan indication for treating Hypertrophic Cardiomyopathies (HCM). The acquisition of Bristol Myers Squibb (BMS) at a value of US$13 billion is primarily aimed at capturing a target market of approximately 200,000 patients annually within the United States. The officially reported annual list price for this medication stands at US$89,000, with sales projections estimating an impressive US$4 billion within its initial 6 years on the market (*BMS, 2020*). By the conclusion of December 2022, BMS had reported a global net sales figure, indicating a remarkable achievement of US$24 million in less than a year (*BMS, 2023*).

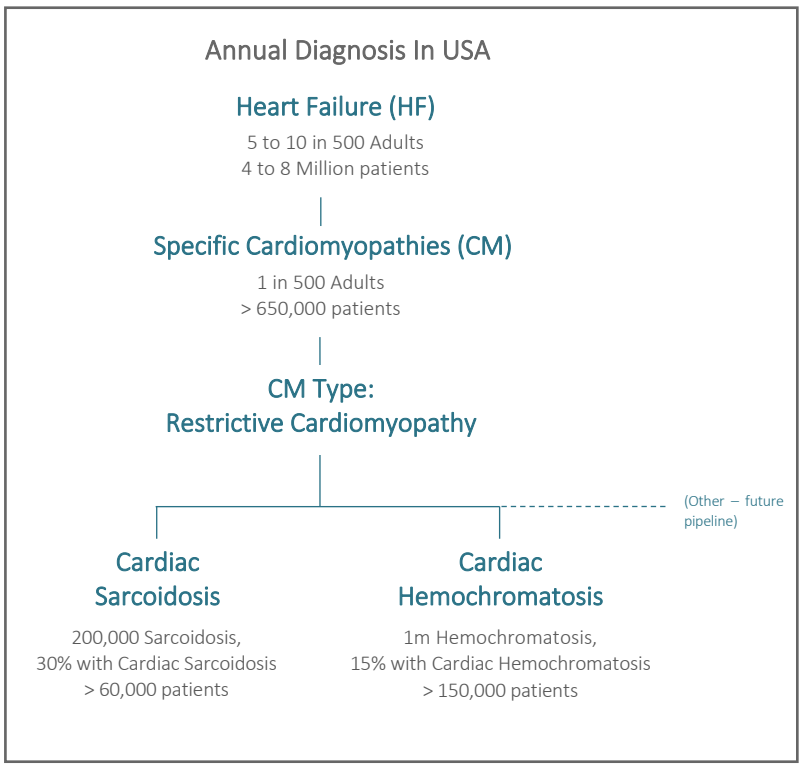


Fig 2.1 ESN Cleer is targeting specific rare disease population with its orphan drug indications

In reference to Camzyos (Mavacamten), ESNtx005 and ESNtx006 is projected to target populations of <100,000 and <200,000 respectively. These are projected to generate combined drug sales surpassing US$ 6 billion within the initial six years following FDA approval.

Market Projection - USA	Mavacamten - FDA Approved 2022 - (market reference)	ESNtx006 (Indication1)	ESNtx005 (Indication 2)
Target Population	< 200,000	< 150,000	< 60,000
Annual List Price**	US$89,500*	US$89,500	US$110,000
TAM	US$18b	US$13b	US$6b
Market Penetration	22%	22%	22%
Projected Sales within 6 years	US$4b	US$3b	US$1.5b
License Upfront	Aug 2020:US$40m		
Regulatory and sales milestone payments	US$147.5m + Royalties		

Market Projection - Europe		ESNtx006 (Indication1)	ESNtx005 (Indication 2)
Target Population		< 200,000	< 40,000
Annual List Price#		US$55,938	US$68,750
TAM		US$11b	US$2.7b
Market Penetration		15%	15%
Projected Sales within 6 years		US$2.4b	US$0.6b

Fig 2.2 ESN Cleer's drug sales projection

(See Annexure 5.1 - Calculations)

3. Key Stakeholders

3.1 Pharmaceutical Challenges in the US [Update Aug '24]

The pharmaceutical sector is facing unprecedented challenges in the US. The following is a summary of the three core factors pharmaceutical companies are battling against. Thus, ESNtx005 is in perfect position to fulfill the gaps from these challenges.

1. **Patent Cliff**
    - Major drugmakers are losing market exclusivity (protection) with imminent patent expirations
    - Major drugmakers expect generic competitors
    - Major drugmakers are projected to lose over US$200 billion annual revenue towards 2030 *(Biopharma 2023)*
2. **IRA**
    - Law in place for drug price reduction. Negotiation started in 2023 with manufacturers for 2026 implementation
        - Drugs of
            - High Expenditure, and
            - No generic competition, and
            - Sales in the market for over 9 years (small molecule)
    - 10 drugs in the market selected for the 1st year, additional drugs for the following years
        - First 10 Drugs Selected
            - Medicare Part D: US$ 50+ billion annual spending in 2022-23
            - 5 of the 10 selected are Cardiovascular drugs
    - Drugmakers' reduced revenue to potentially reach US$450 billion by 2032 *(Tax Foundation 2023)*
3. **Reduced Internal R&D Spending**
    - Reduction of internally developed drugs
    - Cost Advantage with External R&D
    - Q3 2023: 376 M&A deals announced worth US$ 33+ billion
    - 2023 Prescription drug sales: < 40% internally developed *(Evaluate 2023)*

3.2 ESNtx005, Orphan indications in RCM

ESNtx005 is well-positioned to fulfill the gaps of the pharmaceutical challenges (**opportunities**).

1. **New Patent, Market Exclusivity, Not Subjected to IRA**
    - New Orphan Drug
    - Novel Drug patent (Composition of Matter)
    - 20 years patent protection
2. **Low R&D, Regulatory Costs**
    - US Orphan Drugs Act incentives
    - 7 years exclusivity
    - Orphan Drug Tax Credit (ODTC)
    - Clinical Research subsidies
    - Prescription Drug User Fee exemption (US$3m)
    - Fast-Track approval opportunity
3. **M&A Target**
    - Fast Market Access
    - Pivotal Clinical Trial expected within 2 years

3.3 Pharmaceutical Companies

Based on the latest market data released by Evaluate in 2023, the orphan drug market is anticipated to exhibit nearly double the growth rate of the non-orphan market on a global scale, with a Compound Annual Growth Rate (CAGR) projected at 12% for the period spanning 2023 to 2028. This trend is directly linked to the consistent increase in the number of orphan drug approvals granted by the FDA, which has exceeded the approvals for non-orphan drugs over four of the last five years.

The trajectory of orphan drug sales relative to prescription sales is predicted to maintain its upward trajectory for the majority of major pharmaceutical companies. Projections indicate that the market value of orphan drug sales could reach a noteworthy US$300 billion by 2028, accounting for nearly 20% of the total prescription sales.

ESN Cleer is strategically positioned in alignment to the most rapidly expanding segments within the pharmaceutical industry.

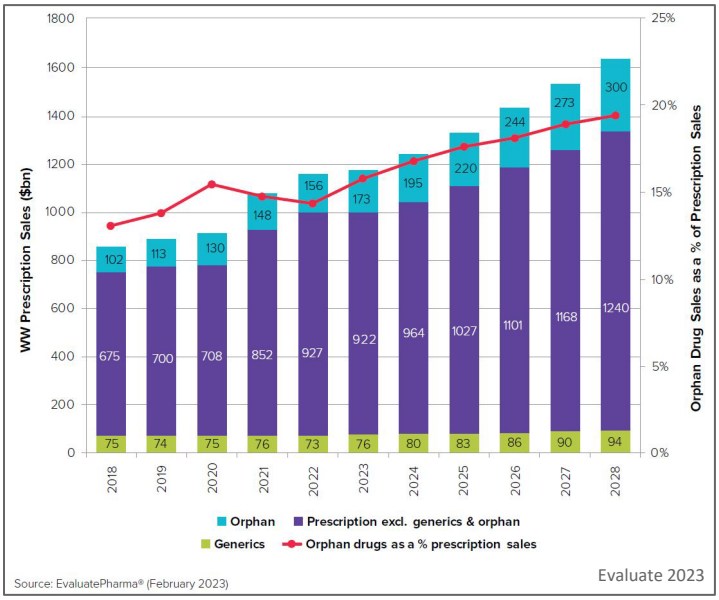


Fig 3.1 Global Orphan Drug Sales & Share of Prescription Drug Market (2018-28)

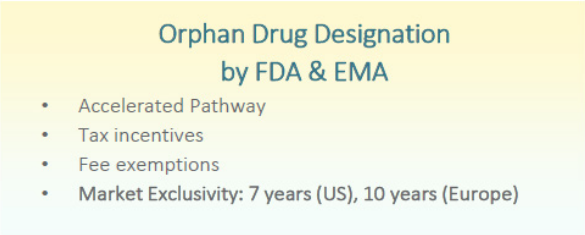


Fig 3.2 Orphan Drug Designation – Key benefits

US Government and Regulatory Support to Orphan Drug Development

The Orphan Drug Act offers substantial incentives to sponsors, primarily pharmaceutical companies, engaged in the development of orphan drugs. *Tables 3.1* and *3.2* present the rationale and outcomes of initiatives led by the US government in the realm of rare diseases and orphan drugs.

Elements	Description	Impact
Rare disease definition	• < 200,000 patients in the United States or • > 200,000 patients but with no reasonable expectation that the cost of development will be recovered*	The intent of the Orphan Drug act is to provide incentives for drug manufacturers to provide treatment for rare diseases
Market exclusivity	• Seven-year market exclusivity for sponsors of approved orphan drugs or products	The market exclusivity for a new chemical entity in the United States is typically five years after FDA approval; for orphan drugs, the FDA will not award market authorization for a generic drug for the rare disease for seven years post-approval, a substantial incentive of superior patent protection
Tax incentives	• The Orphan Drug Tax Credit (ODTC) allows sponsors who have orphan designation to collect tax credit, which is 25% of applicable costs, for expenses occurred subsequent to issue of the designation for U.S. clinical trial costs on the orphan indication	The ODTC lowers the cost of drug development and is particularly beneficial to smaller manufacturers, who without the credit, may not be able to continue their development programs for treatments for rare diseases
Clinical research subsidies	• Orphan Product Grant program provides funding for clinical testing of new therapies to treat and/or diagnose rare diseases**	The grant program lowers the cost of drug development. According to the FDA, the Office of Orphan Products Development (OOPD) has received over 2,500 applications, reviewed over 2,200, funded over 660 studies and helped 70 products gain marketing approval Receiving a grant from the Orphan Product Grant program eases the likelihood of marketing authorization
Other regulatory incentives	• Orphan drugs and products are exempt from the usual new drug application or "user" fees charged by FDA (i.e., PDUFA)	These regulatory incentives lower the cost of drug development and enable therapies to reach patients sooner

Sources: FDA.gov; Cheung R, Kohler J, Illingworth P. Health Law Journal. 2004; NORD Impact of the Orphan Drug Tax Credit on treatments for rare diseases 2015; oig.hhs.gov.

Exhibit Notes: *Only three therapies have received orphan drug designation under this second definition for rare disease.

**Grants are modest and can run approximately $500,000/year.

(IQVIA, 2020)

Table 3.1 Key Elements of the Orphan Drug Act

US FDA Orphan and Non-Orphan Drugs approved 2017-21

Between 2017-21, FDA approved 242 new drugs marketed in the US, 118 (48.8%) orphan and 124 (51.2%) non-orphan.

Orphan drugs vs non-orphan drugs:	Orphan	Non-Orphan
Fist-in-class	59.2%	40.8%
Intended for treatment	50.2%	49.8%
Expedited review process & other regulatory designations	62.4%	37.6%
Priority review designations	74.4%	25.6%
Fast-track designations	59.8%	40.2%

(Healthcare Basel, 2023)

Table 3.2 Orphan vs Non-Orphan Drugs (2017-21)

Aug '24 update

- ***"60% of FDA's new drug approvals in 2023 were orphan designated"***
- ***"For the past five years, FDA's share of orphan approvals has exceeded 50%."***

Evaluate 2024

3.4 Payer

The US government also extends financial assistance to individuals afflicted by rare diseases through substantial subsidies. The primary avenues through which the US government extends support to patients are the Medicare and Medicaid programs. Table 3.4 illustrates the significance of US government spending on orphan drugs.

ESN Cleer is strategically positioned to ensure its orphan drug falls within the purview of government rebate programs.

US Government Prescription Drug Programs:

Medicare (Part D):	Since January 1, 2006, everyone with Medicare, regardless of income, health status, or prescription drug usage has had access to prescription drug coverage.
Medicaid:	Medicaid is a health coverage assistance program for children, adults, pregnant women, people with disabilities, and seniors who qualify due to low income or other criteria.

(US Department of Health)

- **85%** of orphan drugs is on highest cost-sharing tier
- **Less restrictions** for orphan drugs with **single** indications
- Orphan drugs are typically placed in specialty tier, often patients pay up to 40% of drug's full price

(AJMC 2020)

Table 3.3 Medicare & Medicaid Key Notes

US Government Spend on Prescription Drugs in 2021 (US$)

In 2021, the US government spends over US$ 300 billion on prescription drugs, with **US$ 92 billion** (>30%) of the spend are Orphan drugs. **Over 70%** of all approved Orphan Drugs qualify for government subsidies to patients.

	Medicare Part-D		Medicaid	
	Spend	# of Drugs	Spend	# of Drugs
Non-Orphan Drugs	$153,666,035,222	2,870	$56,042,334,809	3,625
Orphan Drugs	$62,042,306,021	696	$30,354,703,393	719
% Orphan Drugs of All Drugs Spend	29%	20%	35%	17%

		US Gov Subsidised
Total Approved Orphan Drugs 1,148	Medicare Part-D	810, 71%
	Medicaid	900, 78%

Table 3.4 US Government Drug Spending

Data Source
Centers for Medicare & Medicaid Services
USFDA Orphan Drugs database
(2021 – most recent data available)

"Medicare is a (US government) federal program that provides health coverage if you are 65+ or under 65 and have a disability, no matter your income. Medicaid is a (US government) state and federal program that provides health coverage if you have a very low income. If you are eligible for both Medicare and Medicaid (dually eligible), you can have both. They will work together to provide you with health coverage and lower your costs." (Medicare Interactive 2022)

4. Commercialisation

Pharmaceutical enterprises utilize mergers and acquisitions (M&A) and in-licensing strategies to leverage the promising preclinical or clinical advancements achieved by smaller developmental firms, as highlighted by *Pistilli in 2022*. These models hold considerable appeal for pharmaceutical companies as they enable the mitigation of substantial initial development expenses and associated business risks. Simultaneously, the acquired or out-licensing entity gains access to capital through upfront payments, which serves to propel its clinical development trajectory, facilitate future commercialization endeavors, enhance revenue prospects, and command a premium valuation uplift. For major pharmaceutical corporations, M&A and in-licensing represent a strategic approach seen as a "sustainable method of pharmaceutical growth."

4.1 Out-licensing Model

ESN Cleer has strategically positioned itself with opportunities to out-license its innovative drug to a prominent pharmaceutical entity, including the early stages of development (such as pre-Clinical to Phase II). This common industry approach would yield upfront "technology access" revenue for ESN Cleer, complemented by ongoing royalty payments. During the initial stages, the licensee could also offer its resources to expedite regulatory processes. As the drug progresses through later clinical development phases, the licensee often secure rights for distribution and marketing, or in many instances, an acquisition may transpire.

This model holds proven appeal for major pharmaceutical companies as it effectively diminishes substantial early-stage development expenditures and business risks. This collaboration extends across international borders, fostering risk mitigation for all parties involved, particularly in cross-border engagements like those with US and China. It's important to note licensing and collaborative expenditure by major pharmaceutical has increased, as evidenced by the recent uptick in upfront expenses observed in the market in 2021 (*Brown, Elmhirst, 2022*). Notably, more than half of China's 181 biotech deals in 2021 involved in-licensing from overseas sources (*Yinn, 2022*).

ESN Cleer's strategic blueprint encompasses access to global markets throughout licensing arrangements with major pharmaceutical companies in regions such as the US, Europe, China, and the broader Asia-Pacific area.

Recent Out-License Successes

In 2019, Novartis entered into a licensing agreement with Akcea Therapeutics to acquire the rights for the cardiovascular drug TQJ230, which was in a pre-Phase III stage of development. The upfront payment made by Novartis amounted to US$150 million, and the agreement also encompassed potential royalties, licensing fees, and milestone payments, ultimately culminating in a substantial deal worth up to US$1.6 billion (*Akcea, 2019*). In a subsequent development, Akcea Therapeutics was acquired by Ionis Pharmaceuticals later in 2020.

Another noteworthy recent instance of a significant licensing agreement involved the clinical-stage company Ashvattha Therapeutics. In April 2022, Ashvattha secured an upfront payment of US$30 million from Huadong, alongside commitments for future royalty payments pertaining to forthcoming licensed products. Following this milestone, Ashvattha successfully increased its total Series B funding to a sum of US$69 million (*Ashvattha, 2022*).

4.2 Mergers & Acquisitions

ESN Cleer is positioned to draw interest from merger and acquisition (M&A) prospects as it advances through its clinical development stages, akin to the enterprises outlined in *Figure 4.1* (*Evaluate, 2019*).

The list highlights prominent pharmaceutical firms that have engaged in substantial M&A transactions spanning the years 2010 to 2019. Each of these companies is engaged in either ongoing clinical development initiatives related to cardiovascular therapeutics or has already introduced cardiac medications to the market. Particularly noteworthy is the acquisition-spin-off model, exemplified by Acceleron's separation from Merck. This development is particularly notable as Acceleron has evolved into Merck's pre-clinical development arm focused on cardiovascular endeavors.

Company	Volume	Value ($bn)	Average ($m)
AbbVie	31	253	8,147
Takeda	27	153	5,671
Bristol-Myers Squibb	24	132	5,509
Merck	20	39	1,973
Novartis	15	66	4,392
Teva	15	61	4,067
Roche	14	22	1,575
Pfizer	13	68	5,224
Sanofi	12	44	3,656
AstraZeneca	11	21	1,876

Source: Biomedtracker®, February 2020

Fig 4.1 Biopharmaceutical Companies Involved in Large M&A Deals (2010-19)

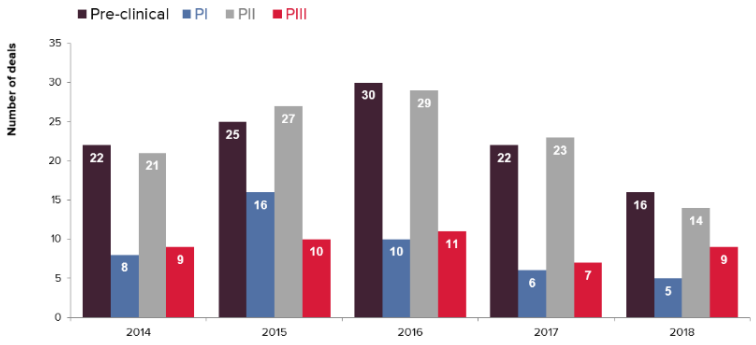


Fig 4.2 Clinical Stage M&A (2014-18)

Figure 4.2 exhibits a prevalent trend wherein the majority of merger and acquisition (M&A) activities occur during the Pre-Clinical and Phase II stages. This trend presents immediate and promising opportunities for ESN Cleer. As depicted in *Figure 4.3*, the trajectory indicates an increase in valuations as clinical development advances. Consequently, the M&A costs for the acquiring company also escalate, mirroring a dynamic where risk decreases while rewards grow with the maturation of development.

An analogous scenario akin to ESN Cleer is represented by Syndesi Therapeutics, a Belgian startup founded in 2018 with an exclusive global license for a range of innovative precognitive SV2A modulators. This entity successfully raised US$20.8 million, attaining a post-money valuation of US$55.8 million. The company, operating in the single-drug clinical development stage, further secured an additional funding of US$56 million spanning 2019 and 2020, culminating in its acquisition by AbbVie in March 2022. This acquisition propelled its valuation to an impressive US$960 million.

Another noteworthy M&A instances encompass Bristol Myers Squibb's acquisition of MyoKardia at a significant US$13 billion, closely aligned with the FDA approval of its pilot drug in April 2021 (*refer to Annexure 5.2 - Case Study: MyoKardia*). Another recent example involves AstraZeneca's acquisition of Cincor for approximately US$1.8 billion at the Phase II stage in February 2023 (*AstraZeneca, 2023*).

Most recent relatable M&A example is the acquisition of Cardior Pharmaceuticals in **March 2024**.

Cardior Pharmaceuticals GmbH is a clinical-stage biopharmaceutical company based in Hanover, Germany. The company is pioneering the discovery and development of RNA-based therapeutics designed to prevent, repair, and reverse diseases of the heart. Cardior's approach primarily focuses on antisense oligonucleotides targeting non-coding RNAs, which regulate critical cellular processes involved in heart diseases. Their lead compound, CDR132L, aims to halt and partially reverse the effects of heart failure by blocking the microRNA molecule miR-132, which is implicated in cardiac dysfunctions.

Novo Nordisk, a Danish multinational pharmaceutical company, has agreed to acquire Cardior Pharmaceuticals for up to €1.025 billion ($1.11 billion). The acquisition deal includes an upfront payment and additional milestone payments based on the achievement of certain development and commercial milestones.

Key Aspects of the Deal:

1. Lead Compound - CDR132L:
   - CDR132L is currently in Phase 2 clinical development for heart failure with reduced ejection fraction (HFrEF). The compound has shown promise in improving cardiac function in Phase 1b trials and is designed to target the microRNA miR-132, which is involved in heart disease pathology.
   - Novo Nordisk plans to initiate a second Phase 2 trial to investigate CDR132L in a population with chronic heart failure and cardiac hypertrophy.

2. Strategic Importance:
   - The acquisition aligns with Novo Nordisk's strategy to expand its cardiovascular pipeline, complementing its existing focus on diabetes and weight-loss therapies.
   - The deal reflects Novo Nordisk's commitment to becoming a leader in cardiovascular disease treatment, leveraging Cardior's innovative RNA-based therapeutic approaches.

3. Financials and Timeline:
   - The transaction is expected to close in the second quarter of 2024, subject to regulatory approvals and other customary conditions.
   - The acquisition will be funded from Novo Nordisk's financial reserves and will not impact the company's previously communicated operating profit outlook for 2024.

Impact and Future Plans: The acquisition of Cardior Pharmaceuticals by Novo Nordisk is seen as a significant step in advancing novel treatments for heart failure. Novo Nordisk's resources and expertise are expected to accelerate the late-stage development of CDR132L, potentially bringing a first-in-class therapy to market. This move also highlights Novo Nordisk's broader strategy to diversify and strengthen its portfolio in the cardiovascular disease space.

Sources: GlobeNewswire 3/24, Investopedia 3/24, Cardior Pharmaceuticals 3/24, MedCity News 3/24

4.3 Valuation

"Cardiac and Vascular Disorders sector is one of the most active sectors for investors, with an overall funding of USD 42.7B in 2.7K companies. It is also interesting to note that more than one third of the funding has been raised in the last 3 years (2020-2022)." (*Tracxn 2023*)

Despite this significant investment, there remains a noticeable gap in drug development concerning orphan disease indications. ESN Cleer has strategically positioned itself to capitalize on this market opportunity with its proprietary drug, fortified by intellectual property protection. The immediate goal is to initiate a Phase II clinical trial within the forthcoming 18 months, a milestone that holds the potential to propel the company's valuation. Built on ESN Cleer's repurposed drug strategy, designed to mitigate risks, costs, and timelines, it is anticipated that the Phase II clinical trial will be successfully completed by 2025, resulting in a substantial increase in valuation.

ESN Cleer's projected valuation is based on the anticipation of two key milestones: the successful completion of the pre-clinical stage and the Phase II trial. Moreover, the prospect of additional valuation premiums comes into play through potential M&A and licensing opportunities. During the pre-clinical phase, an understanding of growth potential translates into significant profitability while simultaneously minimizing the costs associated with acquisition or licensing. On the other hand, as Phase II generates efficacy data that mitigates substantial risks, the cost for an acquiring company or licensee to engage in acquisition or licensing will likely escalate.

Fig 4.3 illustrates biopharma companies' valuation with the lead drug (new molecules) development stages, based on 311 biopharma's data throughout the period 2005 to 2020 (*Michaeli 2022*).

Company Valuation (mean, US$m)	
Pre-Clinic	88
Phase I	399
Phase II	734
Phase III	1,656
Approved	2,496

Table 4.1 Mean Values of Company Valuations at Different Clinical Development Phases

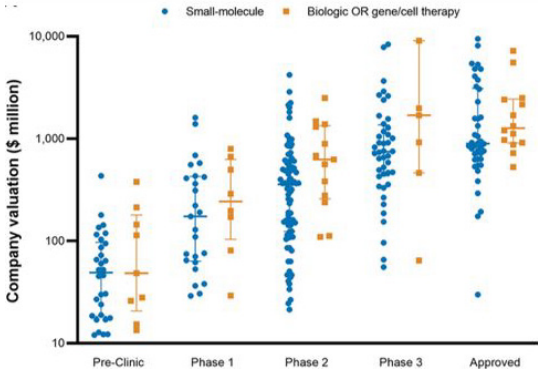


Fig 4.3 Company Valuation at Clinical Development Phases

Cardiovascular initiatives have attained significant market value due to the ongoing trend of global pharmaceutical companies seeking external sources for novel cardiovascular solutions, given the limited options available within the market (*BiopharmaDive, 2020*). ESN Cleer's strategic repurposed drug approach has enabled a streamlined clinical development process, characterized by minimized risks, reduced costs, and shortened timelines to achieve crucial clinical milestones.

Comparable valuations to ESN Cleer include pre-clinical entities such as Haya Therapeutics, which garnered a valuation range of US$66-99 million in May 2022 (*Dealroom, 2022*). Focused on Cardiac fibrosis, Haya Therapeutics is positioned to conduct a Phase I clinical trial between 2022 and 2024. The company's leading candidate, an antisense therapy targeting lncRNA for heart failure treatment, is currently undergoing pre-clinical development (*Businesswire, 2022*).

Established in 2018, Cincor Pharma initially secured exclusive global rights to an innovative aldosterone synthase inhibitor (ASI) compound for its clinical development, particularly in the treatment of resistant hypertension and primary aldosteronism. This endeavor led Cincor to amass US$50 million through its Series A financing in 2019, earmarked for advancing its Phase 2 clinical trials (GlobeNewswire, 2019). Subsequently, Cincor achieved remarkable success by raising US$143 million in its 2021 Series B funding round, culminating in an IPO listing (NASDAQ: CINC) in January 2022. This achievement propelled the company's valuation to a substantial US$584 million (*Crunchbase-Cincor*). See *Section 5.5*, examples of several leading organisations with orphan drugs in development.

5. Annexure

5.1 Total Addressable Market - Calculations

Total Addressable Market Value (USD)					
		Market Projection - USA	Mavacamten	ESNtx006 (Cardiac Hemochromatosis	ESNtx005 (Cardiac Sarcoidosis)
	a)	Target Population (US)	200,000	150,000	60,000
	b)	Annual List Price	$ 89,500	$ 89,500	$ 110,000
	c) = a) x b)	TAM	$ 17,900,000,000	$ 13,425,000,000	$ 6,600,000,000
	d)	Market Penetration	22%	22%	22%
	e) = c) x d)	Projected Sales within 6 years	$ 3,938,000,000	$ 2,953,500,000	$ 1,452,000,000
			US$4b	US$3b	US$1.5b
					US$4.5b
		Market Projection - Europe		ESNtx006 (Cardiac Hemochromatosis	ESNtx005 (Cardiac Sarcoidosis)
	a)	Target Population (EU)		200,000	40,000
	b)	Annual List Price (average US is 1.64 times higher)		$ 55,938	$ 68,750
	c) = a) x b)	TAM		$ 11,187,500,000	$ 2,750,000,000
	d)	Market Penetration		15%	15%
	e) = c) x d)	Projected Sales within 5 years (EMA approval 1 yr after FDA approval)		$ 1,678,125,000	$ 412,500,000
				US$2.4b	US$600m
					US$3.0b

Table 5.1 TAM Calculations

Mavacamten Data Source
Upham 2022

5.2 Case Study I: MyoKardia

Key Aspects of MyoKardia's Strategy (in comparison to ESN Cleer):

- MyoKardia's overarching vision encompassed the development of targeted therapies for addressing a range of rare cardiovascular diseases. This vision was supported by a solitary licensed compound, initially centered around treating obstructive hypertrophic cardiomyopathy (oHCM).
- Over the course of clinical development, MyoKardia focused on specific patient populations, ultimately defining their lead indications as obstructive and non-obstructive cardiomyopathy.
- This approach allowed MyoKardia to efficiently allocate resources for clinical development, with relatively low participant numbers and concise trial durations, compared to the demands of new drug development (See *Table 5.2*).
- Following the success of their initial indications, MyoKardia went on to broaden their drug pipeline with additional candidates.
- The initial indications alone held substantial sales potential for MyoKardia.
- MyoKardia strategically aligned their strategy with the therapeutic focus of major pharmaceutical companies (e.g., cardiovascular health). This strategic alignment facilitated an expansion from their initial targeted indications to include a broader pipeline.

ESN Cleer's commercialization strategy shares similarities with MyoKardia's approach.

	MYK-491	**ESNtx005* (repurposed drug)**
Phase 1 (123 patients)	< 2 years	Reduced / NA
Phase 2 (21 patients)	15 months	15 months
Phase 3 (251 patients)	23 months	23 months
Total	< 5.5 years	< 4 years
Market Projection		
Target Population (US)	< 200,000	118,000
Annual List Price	US$89,500**	
Projected Sales within 6 years	US$4b	> US$2.4b
License Upfront	Aug 2020: Lianbio US$40m	US$40m
Regulatory and sales milestone payments	US$147.5m + Royalties	US$147.5m + Royalties

Table 5.2 MKY-491 and ESNtx005 Projected Comparatives

* Excludes Fast Track or Priority Review designation, see Section 5.4

** Assume ESNtx005 at same price as Camzyos

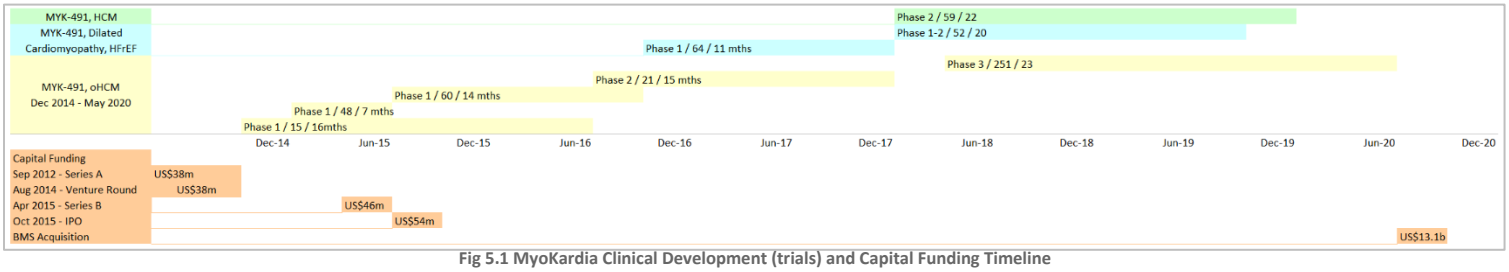


Fig 5.1 MyoKardia Clinical Development (trials) and Capital Funding Timeline

Brief history of MyoKardia

MyoKardia originated from a research collaboration with Cytokinetics in 2012, a partnership that involved the patent assignment rights to Cytokinetics' cardiac sarcomere inhibitor program, geared towards addressing hypertrophic cardiomyopathies (HCM) (*Cytokinetics, 2012)*.

MyoKardia's strategy for tackling HCM through their sarcomere inhibitor (MYK-491) centers around mitigating hypercontractility due to genetic variants, particularly the beta-cardiac myosin, a mechanoenzyme driving ventricular contractions. Typically, HCM affects the inner walls of the left ventricle (LV), leading to increased stiffness, heightened contraction, and reduced relaxation between contractions. This dynamic results in a diminished supply of oxygenated blood pumped throughout the body. MyoKardia's drug, mavacamten (also known as MYK-491), has a specific focus on addressing obstructive HCM (oHCM). In this condition, the septum thickens, causing the LV's outflow tract to narrow, potentially leading to backflow into the left atrium. The severity of oHCM varies depending on the patient's level of physical activity.

Over time, Mavacamten's targeted patient cluster was developed through the refinement of inclusion and exclusion criteria during its Phase II and III clinical trials. Despite FDA approval, the patient cluster for Camzyos (mavacamten's trade name) is expected to be narrower than the reported count of 200,000 oHCM patients in the United States and Europe (*BMS, 2020*). *Fig 5.2* provides an overview of the limitations associated with Camzyos.

Only approved for

- symptomatic obstructive HCM with normal left ventricular systolic function
- Could cause HF, “the squeeze function of the left ventricle should become mildly less vigorous”… “those that did have the adverse reaction recovered when the medication was discontinued”
- According to the FDA, patients who have a serious intercurrent illness (such as a serious infection) or arrhythmia (atrial fibrillation or other uncontrolled fast heart rhythm abnormality) are at greater risk of developing impaired heart muscle contraction and heart failure with mavacamten. Patients must also avoid certain prescription and over-the-counter medicines that interfere with the metabolism (breakdown) of mavacamten.
- The monitoring described by Saberi isn’t optional — it’s part of the Camzyos Risk Evaluation and Mitigation Strategy (REMS), and prescriptions for the drug can only be written by providers who are enrolled in the REMS program.

Fig 5.2 Warnings and Conditions for Camzyos (Uphan 2022)

In October 2020, Bristol Myers Squibb (BMS) completed the acquisition of MyoKardia, a company in the clinical development stage, for a sum of US$13.1 billion. The acquisition was predicated on the expectation of submitting the drug Camzyos for FDA approval in the first quarter of 2021. The approval from the FDA for Camzyos was ultimately secured on April 28th, 2022. BMS has projected its sales to reach the US$4 billion mark by the year 2029 (*Gardner, 2022*), with an annual list price reported at US $89,500 (*Upham, 2022*).

Although the initial indication is confined to a patient cluster of fewer than 200,000, BMS has strategically positioned mavacamten for potential expansion into additional indications. As stated by BMS in 2020, "Bristol Myers Squibb expects to explore the full potential of mavacamten in additional indications, including non-obstructive HCM, as well as develop MyoKardia’s promising pipeline of novel compounds, including two clinical-stage therapeutics: danicamtiv (formerly MYK-491)." This strategic intent is evident through the ongoing implementation of additional mavacamten projects as seen in BMS' progressing pipeline of clinical trial records.

Title / Acronym	Conditions	Intervention / Treatment	Phases / Enrolment	Start / Completion	Duration (mths)	Results (End Points)
Clinical Study to Evaluate Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy / EXPLORER-HCM	Obstructive Hypertrophic Cardiomyopathy	Drug: mavacamten Drug: Placebo	Phase 3 251	May 2018 May 2020 FDA Approval Grated: Apr 2022	23	(FDA) At the end of the study, 37% of participants treated with Camzyos improved on an endpoint measuring exercise capacity and symptoms, compared to 17% of participants in the placebo group. PRIMARY: Participants achieving a clinical response SECONDARY: 1. Post-exercise LVOT gradient 2. pVO2 as Assessed by CPET 3. Proportion of Participants With at Least 1 Class Improvement in NYHA Functional Class 4. Participant-reported Health-related Quality of Life as Assessed by the KCCQ Score 5. Participant-reported Severity of HCM Symptoms as Assessed by the HCMSQ Score
A Phase 2 Open-label Pilot Study Evaluating MYK-461 in Subjects With Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction / PIONEER-HCM	Cardiomyopathy, Hypertrophic Obstructive|Left Ventricular Outflow Tract Obstruction	Drug: MYK-461	Phase 2 21	Aug 2016 Nov 2017	15	PRIMARY: Post-exercise Peak LVOT Gradient SECONDARY: 1. Post-exercise Peak LVOT Gradient 2. Dyspnea Symptom Score 3. Peak VO2 4. VE/VCO2 5. Resting LVEF 6. LV Fractional Shortening (LVFS) 7. Global Longitudinal Strain (GLS) 8. Post-exercise Peak LVOT Gradient from week 12 to 16
Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Oral Doses of MYK-461 in Healthy Volunteers	Healthy	Drug: MYK-461 Drug: Placebo	Phase 1 60	Aug 2015 Oct 2016	14	PRIMARY: Safety as measured by the incidence of adverse events SECONDARY: pharmacokinetic parameters (X6)
Single Ascending Dose Study of MYK-461 in Healthy Volunteers	Healthy	Drug: Placebo Drug: MYK-461	Phase 1 48	Jan 2015 Jul 2015	7	PRIMARY: Safety as measured by the incidence of adverse events SECONDARY: pharmacokinetic parameters (X4)
Study Evaluating the Safety, Tolerability and Preliminary Pharmacokinetics and Pharmacodynamics of MYK-461	Hypertrophic Cardiomyopathy	Drug: MYK-461	Phase 1 15	Dec 2014 Apr 2016	16	PRIMARY: Safety as measured by the incidence of adverse events SECONDARY: pharmacokinetic parameters (X4)

Table 5.3 Summary of Mavacamten (MYK-461 / Camzyos) – Pivotal Clinical Trials (SOURCE: CLINICALTRIALS.GOV)

IN SUMMARY:

- BMS acquisition Oct 2020, with "demonstrated clinically meaningful results in the pivotal Phase 3 EXPLORER-HCM trial"
- In Nov 2021, expected delayed Jan 2022 FDA approval due to "review updates on Bristol's REMS program"
- FDA Approval Granted: Apr 2022 - BMS forecast reaching $4 billion in sales by 2029
- By Dec 2022 (< 8 mths post-FDA-approval), reported sales reached US$24m globally
- European Commission Approval received: June 2023

		US$ m
Oct 2015	IPO	54
Apr 2015	Series B	46
Aug 2014	Venture Round	14
Sep 2012	Series A	38

Table 5.4 Summary of MyoKardia's Funding Rounds before BMS' 2020 Acquisition

(SOURCE: CRUNCHBASE-MYOKARDIA)

5.3 Case Study II: Tafamidis

Key Milestones in the Development and Commercialization of Tafamidis (in comparison to ESN Cleer):

- Initiation of research and development activities in the 1990s.
- The establishment of FoldRx, a drug discovery and clinical development firm, in 2003, marked the entry of Tafamidis into the clinical development phase.
- FoldRx was subsequently acquired by the global pharmaceutical leader Pfizer in 2010.
- Tafamidis's original target indication was in neurology, specifically for the treatment of TTR-FAP. However, it faced a setback when it was rejected by the FDA in 2012 due to inadequate efficacy results in meeting the clinical trial endpoint.
- Tafamidis took a significant shift as it was repurposed for cardiovascular application, specifically for TTR-CM. This repurposed iteration gained notable regulatory designations, including:
    - Fast Track review status
    - Orphan drug designation
    - First-In-Class drug designation
    - FDA approval in 2019

  Consequently, Tafamidis received FDA approval in 2019 for its new indication.

ESN Cleer's repurposed drug is on a similar pathway to Tafamidis – a repurposed orphan drug for a specific cardiomyopathy indication.

Mechanism of Action:

Genetic mutations or natural misfolding of transthyretin destabalizes transthyretin tetramers, leading to their dissociation and aggregation in tissues, and disrupting the normal function of these tissues. Tafamidis binds to transthyretin tetramers at the thyroxin binding sites, stabilizing the tetramer, reducing the availability of monomers for amyloidogenesis.

Source: Drugbank

Original Indication:

TTR-FAP (Neurology)

Transthyretin Familial Amyloid Polyneuropathy

- A nervous system disease with too much amyloid build up in your body's organs and tissues.
- A progressive disease which requires liver transplant treatment.
- Symptoms include excess amyloid protein in the nerves that branch out from your brain and spinal cord; with disability on sensory, mobility, hearing and vision. Body action control disability includes blood pressure, heart rate, and digestion.
- Life-threatening symptoms include enlarged heart and irregular heartbeat.

Source: WebMD

Approved Indication:

ATTR-CM (Cardiovascular)

Transthyretin Amyloidosis Cardiomyopathy

* Liver produces faulty transthyretin (TTR) proteins, leading to build up of abnormal proteins (fibrils) in the heart's main pumping chamber. The left ventricle becomes stiff and weak, causing difficulties to pump blood to the body, leading to Cardiac Amyloidosis, towards Heart Failure syndrome.

- A progressive disease which requires liver transplant treatment.

Source: Cleveland Clinic

Table 5.5 Tafamidis mechanism of action and before/after repurposed indications

Title / Acronym	Conditions	Intervention / Treatment	Phases / Enrolment	Start / Completion	Duration (mths)	Results (End Points)
The Effect Of Tafamidis For The Transthyretin Amyloid Polyneuropathy Patients With V30M Or Non-V30M Transthyretin	Transthyretin Familial Amyloid Polyneuropathy	Drug: tafamidis	Phase 3 10	Nov 2011 Feb 2014 FDA Rejected June 2012 (*PharmaTimes 2012*)		PRIMARY (1): Number of Participants With Transthyretin (TTR) Stabilization at Week 8 Compared With Baseline as Measured by a Validated Immunoturbidimetric Assay [Time Frame: 8 weeks] SECONDARY(7): [Time Frame: up to Week 78] *Source: ClinicalTrials-Taf1*
Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy (ATTR-ACT)	Transthyretin (TTR) Amyloid Cardiomyopathy	DRUG: Tafamidis|DRUG: Tafamidis|DRUG: Placebo	Phase 3 441	Sep 2013 Jul 2018 FDA Approval Granted: May 2019 *(FDA-Taf)*		PRIMARY (1): Hierarchical Combination of All-Cause Mortality and Frequency of Cardiovascular-Related Hospitalizations [Time Frame: Baseline up to Month 30] SECONDARY (6): [Time Frame: up to Month 30] *Source: ClinicalTrials-Taf1*

Table 5.6 Tafamidis pivotal Phase III clinical trials

		US$ m
Sep 2010	Acquired by Pfizer	Undisclosed
Jun 2010	Venture Round	29
May 2006	Series B	43
Jan 2004	Series A	16

(Source: Crunchbase-FoldRx)

Table 5.7 Summary of FoldRx's Funding Rounds before Pfizer's 2010 Acquisition

Pfizer Reported Annual Sales (US$m)	
2022	2,447
2021	2,015
2020	1,288
2019	473

(Source: Pfizer-Filings)

Table 5.8 Pfizer's Annual Sales from Vyndaqel/Vyndamax (FDA Approved ~ End of 2022)

5.4 ESN Cleer Development Timeline

ESN Cleer's strategy for drug repurposing is poised to considerably shorten its development timeline relative to conventional drug development, thereby substantially mitigating the associated risks, time investment, and financial expenditure on the path to commercialization opportunities.

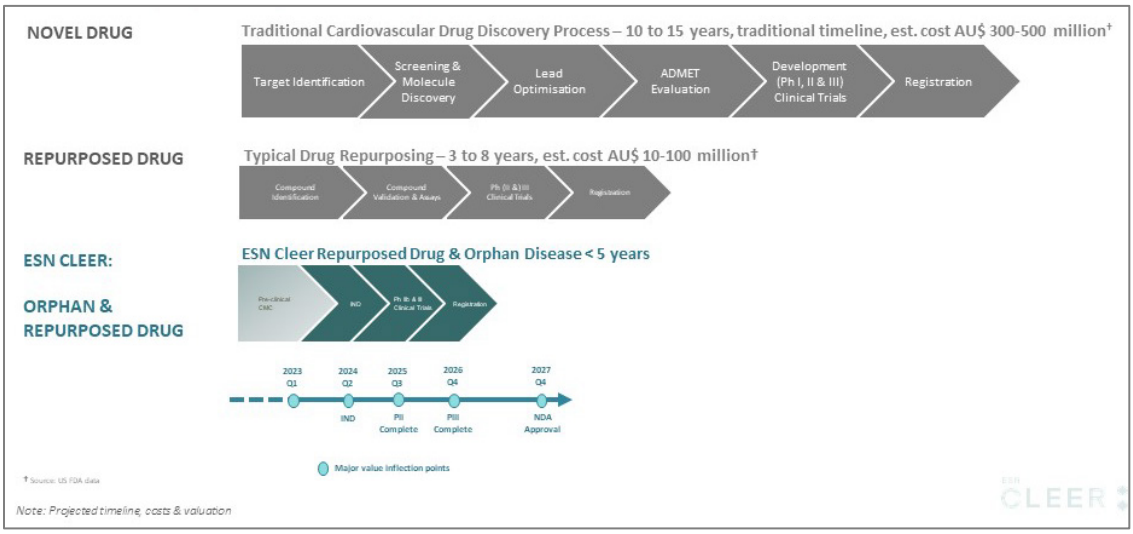


Fig 5.3 Drug Development Timeline – In Comparison

Since the 1980s, global regulatory bodies have implemented mechanisms aimed at expediting the review and approval of pharmaceuticals, thereby enhancing access to novel therapeutic solutions for underserved patient populations. ESNtx005 has the potential to receive such designations from regulatory agencies, such as the FDA, which could facilitate an expedited regulatory evaluation and approval process.

Fast Track (FDA)

The FDA Fast Track Program is specifically designed to streamline the development and hasten the evaluation of novel therapeutics aimed at addressing severe medical conditions with unmet needs. This designation entails more frequent interactions with the FDA to discuss developmental progress and may confer eligibility for Accelerated Approval, Priority Review, and Rolling Review processes. Accelerated approval expedites the provision of evidence demonstrating positive therapeutic clinical benefits, often relying on surrogate or intermediate clinical endpoints such as biomarkers or laboratory measurements. Priority review designation reflects the FDA's commitment to completing its review within a 6-month timeframe, as opposed to the standard 10-month review period. Rolling Review may also permit the incremental submission of a Biologic License Application (BLA) or New Drug Application (NDA) to the FDA for ongoing assessment, rather than submitting the entire final dataset all at once (*USFDA 2018*).

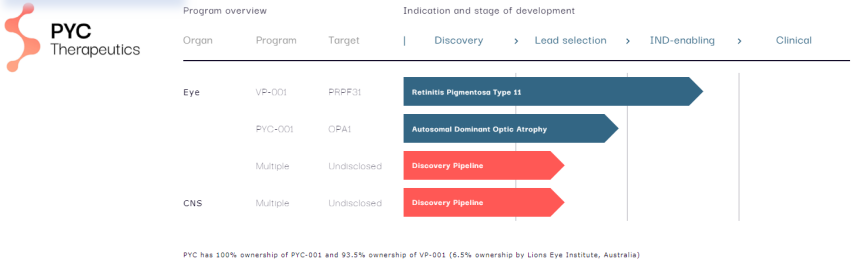
Pfizer's Vyndaquel (tafamidis meglumine), a recent breakthrough in the treatment of a rare cardiovascular disease, has earned Fast Track designation. It was granted Priority Review in January 2019 and received FDA approval by May 2019. Vyndaquel is an oral medication designed to address Hereditary Transthyretin-Mediated Amyloidosis (ATTR-CM), a condition in which the liver produces malfunctioning transthyretin (TTR) proteins. This leads to the accumulation of abnormal proteins in the heart's main pumping chamber, resulting in the left ventricle becoming too stiff and weak to effectively pump blood throughout the body. ATTR-CM represents a rare form of cardiomyopathy. The drug operates as a transthyretin stabilizer, working by binding to the TTR protein to prevent its disintegration, thereby slowing down the progression of the disease. ATTR-CM affects approximately 100,000 patients in the United States, with an annual list price of $225,000. Patients have the possibility of receiving financial assistance through private health insurance, government programs such as Medicare/Medicaid (refer to Table 3.3), or Pfizer's VindaLink financial assistance program.

ESN Cleer is strategically positioned to pursue the FDA's Fast Track designation, aligning with the agency's guiding principles for expediting the accessibility of drugs to patients.

5.5 Valuation Reference

ESN Cleer's approach shares several key components with prominent orphan drug development companies presently operating in the Australian market.

Orphan Indication

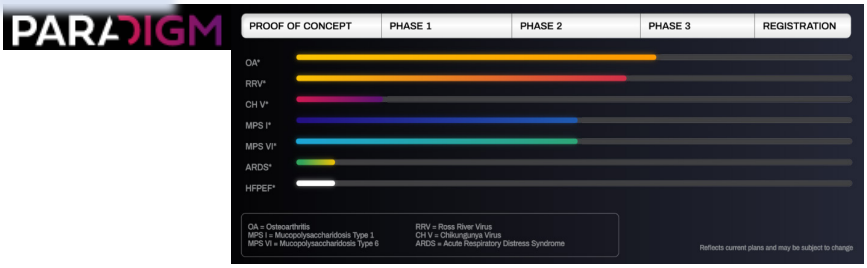


PYC Therapeutics Ltd (ASX: PYC), at pre-revenue focused on developing therapies for inflammatory diseases treatment.

Most advanced development progress: IND enabling stage towards clinical trials.

Market Capitalisation: AU$ 280m

Orphan Indication

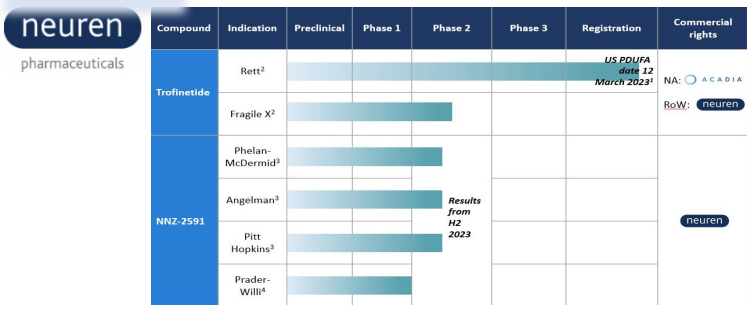


Paradigm Biopharmaceuticals (ASX: PAR), a pre-revenue drug repurposing company with its lead pharmaceutical compound for bone marrow edema.

Most advanced development progress: Phase III clinical trial.

Market Capitalisation: AU$ 385m

Orphan Indication



Neuren Pharmaceuticals are developing several orphan disease programs with their lead program at registration/approval stage.

Market Capitalisation: AU$ 1.6b

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