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10th August 2023

Destiny Pharma

Building An Infection Prevention Powerhouse

Intron Health

Sponsored Research

10/08/2023

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Building an Infection Prevention Powerhouse

INITIATION

Price: £0.54
Target Price: £1.20

Destiny Pharma (DEST) is an LSE-listed Biotech specialising in preventative medicine, with two P3 ready drugs. XF-73 is a novel antibacterial with a rapid and unique onset of action and best-in-class resistance profile, with positive Phase 2b data in preventing post-surgical site infections. NTCD-M3 is a non-pathogenic strain of *C. difficile*, designed to prevent *C. diff* infection (CDI) recurrence by crowding out pathogenic forms of the bacteria. With best-in-class P2 data, Sebela acquired the US rights in Feb-23 and will fully fund P3. A 2023 fundraising extended Destiny's runway to H224, but we expect new deals to extend this further, with a focus on securing a large upfront for the XF-73 out-licensing. With non-risk adj. peak sales of £900m for the 2 drugs, our SOTP values DEST at £1.20/share.

XF-73 Hit Microbiological Endpoint in P2; Predictive of P3 Efficacy

Discovered by Destiny's XF platform, XF-73 killed >99% of *S. aureus* colonies at P2 with strong safety. Convenient dosing (24hrs vs 5 days for mupirocin) can improve compliance and provides surgical flexibility while reducing hospital expenditure. FDA/EMA talks have confirmed P3 design

Targeting a Large Commercial Opportunity in MRSA Prevention

XF-73 has been shown to kill bacteria in under 15 minutes and can be used to decolonise patients in 24hrs pre-surgery. We forecast £620m in non-risk adj. peak sales at just $250/course and 25% US market share.

Sebela Partnership De-risks NTCD-M3 in Preventing CDI

NTCD-M3 has a very strong safety profile and promising efficacy, giving it the potential to outcompete the FMTs in later lines of CDI (*C. difficile* infection) and potentially opening up the first CDI recurrence market. We forecast non-risk adjusted peak sales of £280m with modest penetration.

Considerable Upside Potential to Our Target Price of £1.20/Share

Our SOTP value the two lead assets, assuming both are out-licensed in the US & Europe; we apply very heavy risk adjustments to account for clinical, regulatory and partnership risk. We also deduct opex to 2028.

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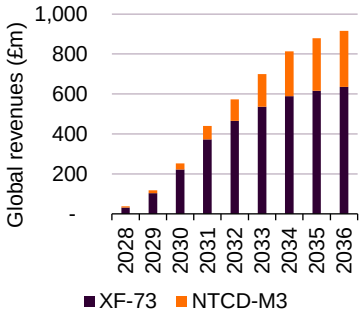
Non-risk adjusted product revenues



Source: Intron Health estimates

Sum-of-the-parts valuation

	NPV/share (£)
NTCD-M3 EU (out-licensed deal)	0.19
NTCD-M3 US (Sebela deal)	0.50
XF-73 (Out-licensed deal)	0.86
G&A to 2028	-0.20
R&D to 2028	-0.19
Net cash (2023)	0.06
Total	**1.22**
Target price	**1.20**
Upside	**2.3x**

Source: Intron Health estimates

Summary Financials

£m	23E	24E	25E	26E
Revenues	0	0	0	0
EPS (£)	-0.07	-0.08	-0.09	-0.10
Net debt (£m)	-6.2	0.6	8.3	17.0
2026 PE		N/A		
Mcap ($m)		66		

Source: Intron Health estimates

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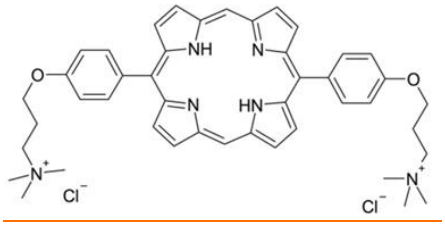
Chart 1: Molecular structure of XF-73



Source: Farrell et al.

XF-73: Destiny's Answer to AMR

Anti-microbial resistance (AMR) is an emerging crisis in healthcare, for which Destiny have developed XF-73 as one of the solutions. XF-73 is not an antibiotic, but an antibacterial drug, used in the prophylactic setting to prevent an infection from ever occurring in high-risk patients undergoing surgery. It has a remarkable antibiotic resistance profile - despite being passaged 55 times in an experimental model, no resistance emerged during preclinical trials. The reason for this stellar resistance profile is likely due to its rapid and unique onset of action, which does not give bacteria long enough to develop resistance before they are killed. Crucially, this means XF-73 could be utilised widely and not held in reserve, as would likely be the fate of a new antibiotic class. In P2 studies, it has generated strong microbiological data, which is recognised by regulators as being strongly predictive of a clinical benefit. Moreover, with nasal decolonisation achieved in 24 hours as opposed to 5 days for standard of care antibiotics, XF-73 could also deliver potential hospital savings and increased throughput. We forecast £185m in heavily risk-adjusted sales by 2035 (£620m non-risk adjusted), leaving open the potential for large upgrades if the programme becomes de-risked (i.e. clinical data readout or partnership terms announced). Destiny is actively seeking a partner to collaborate on the asset's co-development and spearhead its commercialisation efforts.

The XF Platform – Destiny's Antibiotic Generator

Used to discover Destiny's lead asset, the XF Platform is a novel small molecule discovery platform that is designed to specifically generate anti-infective drugs against which bacteria have a very low likelihood of developing resistance. The platform is protected by 85 granted and two pending patents within three patent families, which cover composition of matter, novel mechanism of action and bacterial biofilm action. Of the candidates discovered by the platform, 10-15 have useful activity (i.e. anti-microbial profiles), so there is a high likelihood of future candidates being taken forward.

Table 1: XF platform pipeline and upcoming milestones (timings are Intron estimates)

Asset	Indication	Phase	Upcoming Milestones
XF-73 Nasal	Prevention of post-surgical *staphylococcal* infection	2	Final formulation to complete in H2 2023. Destiny or partner to initiate phase 3 studies in 2024. Potential out-licensing of European rights. Phase 3 study to read out in 2026.
XF-73 Dermal	Treatment of skin infections caused by antibiotic-resistant bacteria associated with open wounds / broken skins	Preclinical	Clinically-enabling GLP study to finish in 2023. Potential out-licensing of global rights in 2023 or early 2024. Phase 3 study to initiate in H1 2024 & read out in 2026.
XF-73 Drugs Research/ Biofilms	Treatment of antibiotic resistant biofilm and bacterial aggregate associated infections	Preclinical	

Source: Company reports

Key benefits of XF-73 include:

- **Ultra rapid bacteria kill** – XF generated assets are faster acting than standard antibiotics in use and kill bacteria in under 15 minutes
- **Ability to kill bacteria in any growth phase** - XF drugs can kill bacteria even when dormant
- **Ability to kill bacteria within bacterial biofilms** – Biofilms act as a protective barrier and can prevent some drugs from being effective
- **Activity against all gram-positive bacteria tested to date and selected gram-negative bacteria – i**ncluding clinically important and infection causing strains
- **No bacterial resistance –** Molecules have a proprietary molecular structure and unique mechanism of antibacterial action, with no signs of bacterial resistance, even after 55 passages (exposures)

Antimicrobial Resistance is an Urgent Global Threat

Antimicrobials are drugs used to prevent or treat infections caused by microorganisms, including bacteria, viruses, fungi and parasites. Their use has caused dramatic reductions in mortality from infectious disease and allows for the possibility of surgery. However, antimicrobial resistance (AMR) is a growing phenomenon, whereby microbes (particularly bacteria) develop resistance against the drugs being used to kill them, stopping the drug from having its intended effect. This is a particular issue with antibiotics given that bacteria can share antibiotic resistant genes very easily. The risk with AMR is that common infections may become difficult or impossible to treat. In light of this, the WHO has declared AMR one of the top 10 global public health threats facing humanity.

AMR is caused by mutations, gene transfer & selective pressure

All organisms mutate as they reproduce – no replication system is perfect. Most changes to genetic code are deleterious and the resulting offspring does not survive, but sometimes a mutation will occur that provides a benefit - such as resistance to an antibiotic in the case of bacteria. In an environment where the antibiotic is highly concentrated, resistance to the antibiotic will create an overwhelming selective pressure. A bacterium with resistance may be the only one to survive and reproduce, which is how AMR initially arises. Once a resistant gene has evolved, it may be spread to other bacteria through gene transfer, enabling other bacteria to become antibiotic-resistant. In places like hospitals, where antibiotic use is high, these strains of bacteria can proliferate quickly and become dominant, out-competing all other strains. This is (un)natural selection in action. The table below highlights some ways that bacteria can develop resistance against antibiotics.

Table 2: Microbes acquire new resistance mechanisms

Resistance Mechanism	Description	Example
Restrict access of the antibiotic to enter the bacteria	Change the design of the cellular doors or limiting the number of them	Gram negative bacteria have an outer membrane that selectively keeps antibiotics from entering
Remove the antibiotic from cell	Use cellular pumps in the cell wall to remove any drugs that enter the cell	Several *candida* species synthesise pumps to get rid of azoles, such as fluconazole
Alter or destroy the antibiotic	Some bacteria use enzymes to degrade the drug	*Klebsiella pneumoniae* bacteria secrete carbapenemase enzymes, which break down carbapenem and most other beta-lactam antibiotics
Change target for antibiotic	Antibiotic drugs are designed to target specific parts of a bacterium. The bacterium can alter the target protein so that the drug can no longer bind to it.	*Aspergillus fumigatus* changes the cyp1A gene so that triazoles cannot bind to the protein
Bypass effects of the antibiotics	Bacteria develop new biochemical pathways that avoid using the drug's target	Some *Staphylococcus aureus* bacteria can bypass the drug effects of trimethoprim

Source: CDC

AMR is a considerable threat, but a solution seems far away

Infections caused by antimicrobial-resistant bacteria result in increased frequency of hospitalisation, prolonged hospitalisation, increased duration of illness and increased mortality, as the antibiotics used are not effective at killing the pathogenic bacteria. More than 2.8 million infections from antibiotic-resistant bacteria occur in the US each year, resulting in 35k deaths. However, without new antibiotics, the toll is expected to grow very materially, underlining the need for new therapeutics. Despite that, the current clinical pipeline of new antimicrobials is scarce. In 2022, the WHO identified only 27 antibiotics in clinical development that target the WHO list of priority pathogens, of which only 6 were considered to be innovative. Moreover, resistance is reported to most new antibiotic agents 2–3 years post market entry, on average, meaning that new antibiotics only postpone the problem. This is where Destiny's XF-73 comes in.

XF-73: Next-Gen MRSA Prevention

Potassium ions are integral to the proper functioning of bacteria, including osmotic pressure regulation, maintaining membrane potential, stabilising DNA and RNA and the activation of enzymes.

Exeporfinium chloride (XF-73) is a novel anti-microbial drug, created and selected as a leading candidate by Destiny's XF platform. It is a di-cationic (carries a positive charge of 2) and porphyrin (consists of four interconnected rings) molecule. It was designed to eliminate gram-positive bacteria such as *S. aureus* through selectively binding to and disrupting the bacterial cell membrane, causing rapid leakage of ATP (a unit of cellular energy) and potassium (see margin), leading to a rapid loss of bacterial cell viability. XF-73 has been formulated into a gel formulation, designed to be applied to patients' noses to kill infection-causing bacteria such as MRSA.

Table 3: Clinical profile of XF-73

Factor	XF-73
Route of administration	Topical nasal gel
Dosing regiment	Administered 4 times into each nostril over 24 hours prior to surgery, and then a single application immediately upon closure of surgical wound
Concentration	0.2% w/w

Source: Company reports

Unique mechanism enables activity against AB-resistant bacteria

XF-73 disrupts the *S. aureus* membrane bilayer and promotes rapid leakage of crucial components for homeostasis (i.e. K+, ATP), without causing cell membrane lysis. While the precise mechanism of action is not yet fully understood, biochemical data strongly suggests that XF-73 operates in a manner distinct from currently available antibiotics. This unique mode of action highlights the potential of XF-73 to combat bacterial strains that have developed resistance to conventional antibiotics:

- Daptomycin – targets cytoplasmic membrane but exhibits a calcium-dependent action
- Nisin – targets cytoplasmic membrane and causes rapid leakage of potassium and ATP
- Vancomycin - inhibits peptidoglycan; XF-73 activity was not impacted by the presence of vancomycin resistance genes (VanA, VanB, VanC)
- Penicillin, cephalosporin, and carbapenem – involves cell wall synthesis; resistance to these antibiotics did not affect the activity of XF-73

High Potential in Post-Surgical *S. aureus* Infections

XF-73 is targeting the prevention of post-surgical *Staphylococcus aureus* infection setting, which is one that has proven difficult to manage and now represents a large unmet medical need. Despite the challenge, based on investigations to date, the drug has demonstrated promising efficacy, safety and convenience in this setting:

- Highly potent at eliminating all strains of *S. aureus*, including MRSA, with up to 99.5% destroyed following treatment
- Fast-acting, with significantly reduced nasal burden compared to mupirocin, which is administered over 5 days vs 24 hours for XF-73
- Strong safety profile: non-irritant, limited systemic absorption and no outstanding side effects
- Easy to administer in the hospital setting
- No evidence of drug resistance, even after 55 passages
- Long product shelf life

S. aureus is linked to a majority of post-surgical infections

Infections can develop following surgical procedures. Research has shown that 70-90% of post-surgical procedures are caused by pathogens already carried by patients. The most common pathogen is *S. aureus*, a gram-positive bacterium that is often found on the skin and in the nose. It has been estimated that 3-5% of people undergoing surgical procedures develop an infection at the surgical site, of which ~25% have

been linked to *S. aureus*. Carriers of these bacteria are 9x more likely to develop staphylococcal infections after surgery, compared to noncarriers.

Resistant strains of *S. aureus* (e.g. MRSA) are very hard to manage

Methicillin-resistant *Staphylococcus aureus* (MRSA) are strains of *S. aureus* that have developed resistance to common antibiotics such as methicillin. Although MRSA was initially identified in the 1960s, recent studies have shed light on its alarming prevalence, with up to 89% of isolated *S. aureus* strains being confirmed as MRSA in some hospitals. Infections caused by MRSA pose significant challenges to treatment algorithms and can lead to the development of more serious conditions. On average, patients infected by *S. aureus* require an extended hospital stay of approximately 15 days, costing >$160,000 per patient.

Nasal Decolonisation Recommended by Guidelines

Reduction of all strains of *S. aureus* can significantly reduce post-surgical infections by up to 60%, and also reduce mortality. As a result, several international guidelines and the CDC all recommend nasal decolonisation with intranasal antibiotics/antiseptics and with full body wash prior to surgeries.

The US Surgical Infection Society (SIS), the Society for Hospital Epidemiologists of America (SHEA), the Infectious Disease Society of America (IDSA), the American Society of Hospital Pharmacists (ASHP), Agency for Healthcare Research and Quality (AHRQ), Journal of the American Medical Association (JAMA)

- All *S. aureus* (including MRSA) carriers should be decolonised in all cardiovascular and most orthopaedic surgeries – recommendation by the SIS, SHEA, IDSA, and ASHP (see margin)
- Patients undergoing high risk surgeries (e.g. cardiothoracic, orthopedic, and neurosurgery) should use an intranasal antistaphylococcal antibiotic/antiseptic (e.g. mupirocin or iodophor) and chlorhexidine wash or wipes prior to surgery – CDC
- All patients treated in the Intensive Care Unit should receive decolonisation without the need for screening (i.e. Universal Decolonisation), which was awarded a Grade I, demonstrating the highest level of evidence rating – recommendation by AHRQ/IDSA/SHEA and are implemented by US hospital groups, including the Hospital Corporation of America
- Perform topical intranasal decolonisation prior to surgery with the highest strength to all cardiac surgical patients, not just for *S. aureus* carriers – updated guidelines published in JAMA in 2020 for US surgeons
- In Europe, there are guidelines (e.g. NICE) in place that recommend the decolonisation of patients who are *S. aureus* carriers before undergoing specific surgical procedures

But mupirocin as the SoC antibiotic may soon be ineffective

In current medical guidelines, nasal decolonisation to prevent surgical infections often relies on the use of the generic antibiotic mupirocin. However, the five day treatment regimen causes 1) compliance issues, 2) problems with scheduling surgery given the inflexibility of the dosing, and 3) an increased risk of developing bacterial resistance. A 2020 review highlighted a concerning rise in resistance rates, with resistance seen for 7.6% of colonies of *S. aureus* and 13.8% for MRSA. We anticipate that the prevalence of mupirocin-resistant strains will continue to rise, severely limiting its effectiveness in reducing surgical infections. Alternative options such as intranasal antiseptics (e.g. povidone-iodine), antiseptic wash (e.g. chlorhexidine), intranasal photo-disinfection, etc, may also be used in combination with mupirocin, but these have not demonstrated a benefit over mupirocin.

A need for next-gen products to overcome bacterial resistance

There needs to be an innovative option to effectively eliminate *S. aureus* strains, including MRSA, to prevent surgical infections. We believe such a product would need to have the following features:

- High efficacy in eliminating *S. aureus,* including MRSA
- Substantial evidence demonstrating there is a low propensity for bacteria to develop resistance
- Fast onset of action which reduces treatment burden and reduces likelihood of building up drug resistance
- Ease of application and fits into current medical guidelines for nasal decolonisation
- Cost effective and does not increase economic burden on the healthcare system

Ph2b Data Showed *S. aureus* Reduction of >99.2%

The phase 2b data that Destiny have generated is very strong in our view, with very clear superiority achieved vs placebo on a microbiological endpoint (a >99% reduction in *S. aureus* colony forming units from baseline, vs 30% for placebo). There is strong evidence that a positive effect on this endpoint is predictive of a clinical benefit (fewer post-surgical infections) and the clinical guidelines reflect this reality. Destiny is now focused on preparing the ground for a phase III programme, which will consist of two studies powered to show clinical benefit vs placebo, expected to initiate in 2024.

A colony forming unit (CFU) is a unit measuring the number of viable microorganisms (such as bacteria). It represents a single microorganism or a group of microorganisms that are capable of forming a visible colony under specific laboratory conditions, typically on a solid growth medium. It is a useful measure for quantifying the viable microbial load.

XF-73 significantly reduced nasal *S. aureus* colonisation

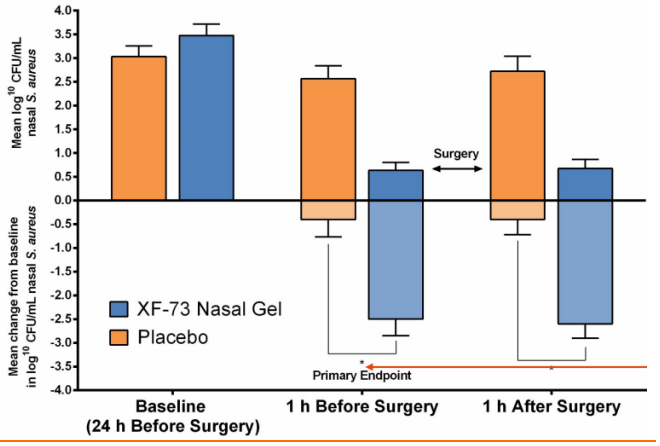
In this phase 2b trial, patients received 4 doses of either XF-73 or placebo in 24 hours prior to surgery and the 5th dose immediately after surgery. The results show XF-73 significantly reduced the number of colony forming units (CFU) for *S. aureus* by 99.2% from baseline to 1 hour before surgery, meeting the primary endpoint. Furthermore, 83.7% of XF-73 treated patients were completely decolonised of nasal *S. aureus* or had a >99% reduction 1-hour ahead of surgery vs just 25% with placebo.

Table 4: Baseline P2b trial info and results for XF-73

Trial	**NCT03915470**		
Trial Design	P2 randomised, double-blind, placebo-controlled		
Patients	Nasal *S. aureus* undergoing cardiac surgery		
N	124		
RoA	Intranasal topical 0.2% (w/w)		
Regimen	XF-73 or placebo for 3 doses in 24 hrs before surgery, 4th dose at 1hr before surgery, and 5th dose at 1hr after surgery.		
MRSA colonisation	3.20%		
Type of cardiac surgery:	Coronary artery bypass graft: 63.8% Mitral valve replacement / repair:16.9% Aortic valve replacement: 16.9%		
Primary endpoint	**XF-73**	**Placebo**	**Significance**
Decrease in S. aureus from baseline (after 3 doses, before surgery)	−2.842 log10	−0.469 log10	P<0.0001

Source: Mangino et al, 2023 ; CFU – Colony Forming Units

Chart 2: Mean change in nasal S. aureus CFU over time



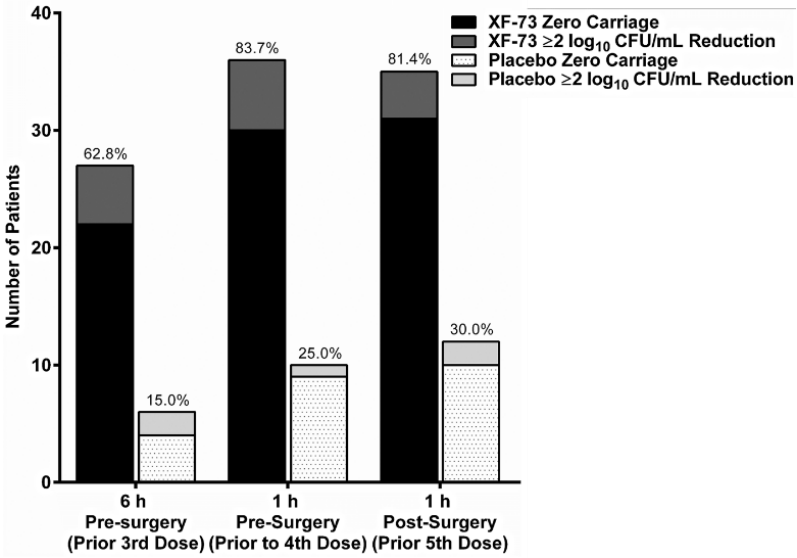
*Source: Company reports; * Difference in mean change from baseline log10 CFU/mL nasal S. aureus, p<0.0001; Mean change in CFU is calculated by the ratio between final CFU and baseline CFU*

- Difference between change in CFU immediately after surgery (after 4 doses and prior to the 5th dose) was also statistically significant with p<0.0001

Robust protection during the most vulnerable period

This XF-73 facilitated decolonisation was maintained through the perioperative period, where the risk of *S. aureus* infection is highest. Within 1 hour of incision closure, the decrease in *S. aureus* was significantly greater in the XF-73 cohort vs placebo, with a least-squares mean difference of −2.2 log10 CFU/mL (p < 0.0001). Post surgery (prior to 5th dose), 81% of patients reported zero nasal *S. aureus* carriage or a 99% reduction, vs just 30% from the placebo arm.

Chart 3: % of patients with zero nasal S. aureus or a >2 log 10 CFU/mL reduction



Source: Mangino et al, 2023; Note: ≥2 log10 change represents the reduction of >99%

Safety data looks very strong, with no adverse signals

In the P2b study, XF-73 was safe and well tolerated. Incidence rates of the most frequently reported TEAEs were similar across both XF-73 and placebo arms, with common AEs including pleural effusion, anaemia, pericardial effusion and atrial fibrillation. No local reactions at the application site (anterior nares) occurred and there were no significant changes in sense of smell.

Table 5: Phase 2 safety data

Safety	XF-73 (n=63)	Placebo (n=61)
Treatment emergent adverse events (Number of cases)	67	68
Serious adverse events	4 (6%)	5 (8%)
Most frequent AEs:		
Pleural Effusion	16 (25%)	14 (23%)
Anaemia	5 (8%)	6 (10%)
Pericardial Effusion	5 (8%)	5 (8%)
Atrial Fibrillation	5 (8%)	4 (7%)

Source: Mangino et al, 2023

Clinical outcomes not tested in P2b; will read out in the phase 3

No surgical site infections were observed in either arm of the study during the 1-month or 3-month follow-up periods, due to the small number of patients. Existing literature indicates that post-surgical infections may occur in 0.5% to 3% of patients, which implies, on average, one infection for every 200 patients treated (at the lower end), whereas in the phase 2 study only 124 patients were treated. The primary endpoint of the phase 2 instead looked at reduction of *S. aureus* CFUs, which is strongly associated with positive clinical outcomes (i.e. fewer post-surgical infections). However, to be approved, XF-73 will need to confirm the reduction in risk of post-surgical infections endpoint in the phase 3 study. As over 80% of post-surgery infection strains are believed to be from the

patient's own nasal carriage, the strong P2 data in reducing the *S. aureus* CFUs leaves us confident that a good P3 readout can be achieved.

Phase 3 to Initiate in 2024

The phase III studies, expected to initiate next year, will recruit enough patients to be powered to show superiority on a clinically significant endpoint (e.g. surgical site infection for treatment vs placebo). This is the regulatory endpoint which will allow Destiny to file for approval following a positive readout. As we have already stated, we are optimistic concerning a phase III readout given the strength of the P2b readout on the microbiological endpoint.

Table 6: Trial design for phase 3 studies required to support filing for XF-73

Factor		
Trial design	Two randomised, double-blind, placebo-controlled Phase 3 trials	
	Study 1	**Study 2**
Indication	Adult patients undergoing **mastectomy with immediate reconstruction or use of tissue expanders** at risk of post-surgical *staphylococcal* infections	Adult patients undergoing **emergency or expedited hip Hemiarthroplasty ("HA") surgery to treat femoral fractures** at risk of post-surgical *staphylococcal* infections
Patient cohort	Patients who have screened positive for *S. aureus*	
Estimated trial start	2024	

Source: Company reports

Preclinical Data is Also Highly Supportive

Destiny have generated preclinical data which demonstrates several of the important advantages of XF-73 over established antibiotics. These include that 1) it is effective against gram positive bacteria in biofilms, and 2) that no resistance develops, even after being exposed 55 times to XF-73. This second feature is remarkable and is likely to be related to the speed of XF-73's action (it has been shown to destroy >99.9% of two different MRSA strains in under 15 minutes). This bacteria killing is faster than the time taken for bacteria to reproduce, which means they would not have time to develop resistance-producing mutations during mitosis.

Effective against biofilms at low concentration

Microbial biofilms in human infections are problematic. Biofilms form when bacteria adhere to a surface and become embedded within self-synthesised extracellular polymeric substances, making the bacteria they encase several 1000-fold less susceptible to antibiotics.

In a minimum biofilm eradication concentration (MBEC) assay, biofilms (see margin) containing *S. aureus* were treated with Destiny's XF drugs and other microbial agents. Biofilm minimum inhibitory concentration (bMIC) was measured as the lowest concentration of antimicrobial agent that inhibited bacterial growth. Following drug removal, any surviving bacteria within the biofilms were washed in saline and transferred to fresh growth media. The bacteria in the biofilms were then allowed to regrow for 24 hours. The assay recorded the concentration at which the drug completely eradicated the biofilms (MBEC) and prevented regrowth. These findings were compared against the minimum concentration of

drug required to kill the bacteria in their “free-swimming” form (Planktonic MIC).

XF-73 demonstrated excellent activity against *S. aureus* biofilms compared to other antimicrobial agents, with a low bMIC and MBEC, with only 1mg/mL required to prevent biofilm planktonic growth and 2mg/ml required to completely eradicate the biofilms and prevent regrowth. The bMIC and MBEC results were within one order of magnitude of the planktonic MIC, suggesting that XF-73 is equally effective against *S. aureus* in the challenging form of biofilms as it is against free *S. aureus* cells in their “free swimming form”.

Table 7: In vitro study results of XF-73 against S. aureus biofilms

Antimicrobial Agent	Planktonic MIC (mg/ml)	Biofilm MIC (mg/L)	MEC (mg/L)
XF-70	1	1	2
XF-73	**1**	**1**	**2**
Cefotaxime	0.5	4	>256
Chlorhexidine	2	1	>256
Ciprofloxacin	2	4	>256
CTAB	2	2	>256
Daptomycin	1	2	>256
Flucloxacillin	0.125	4	>256
Fosfomycin	16	8	>256
Fusidic acid	0.25	0.5	>256
Gentamicin	0.5	1	>256
Meropenem	0.5	0.5	>256
Mupirocin	0.125	0.25	>256
Nisin	2	64	>256
Rifampicin	0.008	0.02	>256
Tetracycline	1	0.5	>256
Vancomycin	1	2	>256

Source: Ooi et al , 2009 Note: CTAB, cetyltrimethylammonium bromide

MICs were determined by microdilution in MHB. bMICs and MBECs were determined in MHB using the Calgary biofilm device.

No observed bacterial resistance

In an *in vitro* study of XF-73 vs standard antibiotics, four strains of MRSA bacteria did not show any signs of bacterial resistance to XF-73, despite 55 repeat exposures (called “passaging”) to the drug (the longest published repeat exposure study on record). In contrast, MRSA developed significant resistance to all 4 comparator antibiotics that were tested. This resistance occurred rapidly in all comparators, except for vancomycin, in which this resistance emerged later.

Table 8: Passage experiment data of 4 strains of MRSA vs XF-73 and antibiotics

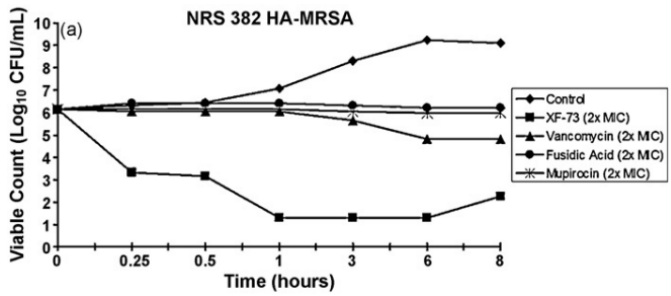
Drug	Number of strains that evolved resistance during passaging	Median number of passages before resistance emergence	Median increase in resistance during passaging
XF-73	**0/4**	**None**	**None**
Vancomycin	2/4	>43.5	6x
Retapamulin	4/4	12	32x
Fusidic Acid	4/4	2	2,048x
Mupirocin	4/4	2	1,200x

Source: Farrell et al, 2011

Fast onset of action reduces probability of developing resistance

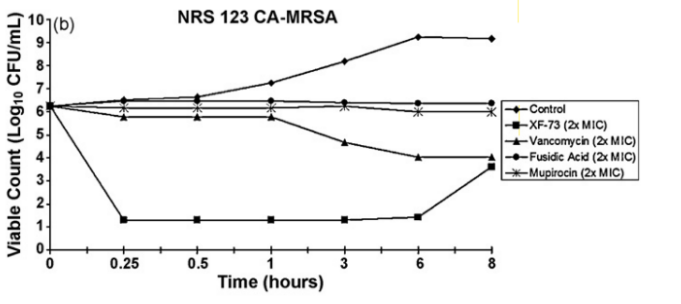
In vitro studies have shown that XF-73 eliminated over 99.9% of MRSA strains (both healthcare-associated and community-associated) within a mere 15 minutes. This rapid onset of action not only ensures swift bacterial eradication, but also minimises the likelihood of resistant gene development through mutation, as 15 minutes is shorter than the time taken for a bacterium to reproduce. It is worth noting that the 15-minute measurement interval in these studies represents the initial point of assessment, indicating the possibility of an even quicker onset of action.

Table 9: Bactericidal activity of XF-73 vs antibiotics in healthcare-associated MRSA strain NRS382



Source: Farrell et al.

Chart 4: Bactericidal activity of XF-73 vs antibiotics in community-associated MRSA strain NRS123



Source: Farrell et al.

Non-lytic action reduces probability of gene transfer

Unlike other bactericides, XF-73 demonstrated a unique characteristic of effectively neutralising bacteria without causing cell lysis. This is significant because cell lysis leads to the release of bacterial genetic material into the environment, increasing the likelihood of resistance developed through mutation and gene transfer. This remarkable capability materially diminishes the probability of resistance formation, in our view.

Synergy with Other Key Antibacterial Treatments

XF-73 was shown to enhance the activity of two antibacterial drugs - Polymyxin B (used to treat life-threatening lung bacterial infections) and Ertapenem (to treat diabetic foot ulcers). In an *in vitro* checkerboard assay, XF-73 was assessed in combination with conventional antibiotics and photodynamic therapy, and bacterial growth analysed. The addition of XF-73 was found to enhance polymyxin B potency 4-fold against *Pseudomonas aeruginosa* and enhance Ertapenem potency 8-fold against MRSA. Both pathogens are classes as a top priority by the WHO. In the antibiotics where synergism was not displayed, XF-73 did not antagonise the efficacy of these regimens. These findings suggest promise for XF-73-antibiotic combinations to treat drug-resistant infections that use lower doses of the antibiotic.

XF-73 Compares Well to Potential Competition

Ondine's Steriwave is the only other asset in development for the prevention of post-surgical *S. aureus* infections and utilises lasers to eliminate *S. aureus* colonies before surgery. However, unlike XF-73, which underwent the gold-standard of assessment in a multi-centre, double-blind, placebo-controlled trial design, Steriwave was only tested in a single centre, single-arm, open-label study and has consequently not generated enough data to win a US approval (though it is approved in the EU and Canada). However, its phase III preparations are underway, so it is at a similar stage of development to XF-73. In its Phase II study, Steriwave demonstrated an 88% reduction of *S. aureus* colonies, compared to 95.3% for XF-73 when evaluated by the same methodology (though cross-trial comparisons should still be interpreted with caution). We believe XF-73 has the potential to deliver best-in-class clinical benefit and become the first approved treatment for this indication in the US.

Table 10: Comparison of XF-73 and STERIWAVE for the prevention post-surgical infection through intranasal decolonisation

Asset	XF-73	STERIWAVE (Device)
Company	Destiny Pharma	Ondine Biomedicals
Classification	Drug (Exeporfinium chloride)	Medical Device + solution containing methylene blue and chlorhexidine antiseptic
Mechanism	Disrupt the membrane and kills *S. aureus*	Use laser to generate reactive oxygen species which disrupts the membrane and kills microbials
Effective against MRSA	Yes	Yes
Likelihood of Resistance build-up	Very low - fast-acting and novel mechanism, free of resistance build-up up to 55 passages	Very low - because of mechanism and fast-acting, though some resistance to chlorhexidine has been demonstrated
COGS	< $5	Unknown
Development Status	Phase 3 in preparation	Approved (EU, Canada) Phase 3 in planning (US)
Dosing Regimen	4 times before surgery and once immediately after surgery	Once before surgery and once after surgery; 5 minutes for each treatment
Phase 2 Trial	NCT03915470	NCT05090657 (BENEFIT-PDT)
Trial Design	Placebo-controlled, multi-centre, double-blind	Single-arm, single-centre, open-label
Types of Surgery	Cardiac surgeries	All types of surgical procedures
N	124	322
% of patients with baseline *S. aureus* colonisation	100%	21%
Number of patients with *S. aureus* and treated with intervention	63	67*
% of patients with significant decrease in *S. aureus* levels	95.3%[1]	88%
Decolonisation post-surgery	~80% decolonisation at least 6 days after surgery	Not reported
Reduction of post-operative surgical site infection	- [4]	66%[2] & 47%[3]

*Source: Company reports; * Intron Health estimates; [1] Estimated value by using the same criteria defined in Ondine's analysis; [2] from Ph2 study compared to historical values; [3]Real-life evidence from one of Canada's largest hospitals – Vancouver General Hospital, results presented in Oct 2022; [4]The Ph2 trial was not powered to evaluate clinical benefit*

- It is important to note that STERIWAVE's Ph2 was conducted as an open-label study, which introduces the possibility of bias in the data, and is not directly comparable to XF-73's Ph2 results
- While XF-73 protects over 80% of patients beyond 6 days after surgery, no comparable data has been reported from STERIWAVE
- The operation of Steriwave requires a machine to be present in each operating room, which is inconvenient and expensive for hospitals

- It also requires disposal light guides, nasal dye solution, swabs and a light source unit, which requires storage and maintenance; all of these incur costs, in contrast to XF-73 nasal gel

Polypid's D-PLEX not viewed as a serious competitor

PolyPid is developing D-PLEX, a new extended release formulation of doxycycline, which is currently in Phase 3 development in preventing infections following abdominal surgery. The asset was previously studied in a Phase 3 trial on preventing infection in cardiac surgeries, but it was discontinued in 2022 citing company "prioritisation reasons". Given this history, we do not view it as a serious competitor to XF-73 without seeing further data.

XF-73 Risk-Adj Peak Sales to Reach £185m by 2035

We show how XF-73 could generate over £185m in heavily risk-adjusted peak sales (£620m when not adjusted for clinical, regulatory and partner risk), even with only a 25% US market share and 18% European market share. We provide a strong value-based justification for our $250/course pricing in the US and assume a 60% discount to this in Europe. However, we do not expect Destiny to self-launch the asset and so we model a high single to low double-digit royalty on net sales, with a $20m upfront and $470m of potential milestones, all of which we calculate to be worth >40% of the total value of the molecule (the partner would pay for R&D). We explain our assumptions on deal structure in more detail in the valuation.

Table 11: XF-73 global revenues forecast

£m	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038
US											
TAM (000s)	7,165	7,237	7,309	7,382	7,456	7,531	7,606	7,682	7,759	7,837	7,915
Market share	2%	6%	12%	19%	22%	24%	25%	25%	25%	25%	25%
Patients (000s)	143	434	877	1,403	1,640	1,807	1,902	1,921	1,940	1,959	1,979
Price ($/course)	250	255	260	265	271	276	282	287	293	299	305
Sales	28	87	178	291	347	390	418	431	444	457	471
Risk-adjusted sales	**8**	**26**	**53**	**87**	**104**	**117**	**125**	**129**	**133**	**137**	**141**
growth		*209%*	*106%*	*63%*	*19%*	*12%*	*7%*	*3%*	*3%*	*3%*	*3%*
Europe											
Market share	1%	2%	5%	9%	13%	15%	17%	18%	18%	18%	18%
Patients (000s)	50	145	365	664	932	1,130	1,293	1,383	1,397	1,411	1,425
Price ($/course)	100	153	156	159	162	166	169	172	176	179	183
Sales	4	17	45	83	118	146	171	186	192	198	204
Risk-adjusted sales	**1**	**5**	**13**	**25**	**35**	**44**	**51**	**56**	**58**	**59**	**61**
growth		*342%*	*158%*	*85%*	*43%*	*24%*	*17%*	*9%*	*3%*	*3%*	*3%*
US + Europe											
Risk adjusted sales	10	31	67	112	140	161	177	185	191	196	202
Royalties to Destiny	**1**	**3**	**6**	**11**	**14**	**17**	**19**	**21**	**23**	**24**	**24**

Source: Intron Health estimates

TAM of ~7 million patients in both the US & Europe

In the US, approximately one in three people in the general population are *S. aureus* carriers, who are at 9x greater risk of post-surgical infections compared to non-carriers. However, guidelines recommend that all patients are decolonised for high-risk surgical procedures, of which around 7.5 million take place each year. Assuming that 90% of such patients do receive decolonisation, that implies a market size of ~7 million patients. By our estimates, the figures in Europe are also very similar.

We assume a 2028 launch and a 18-25% market share by 2034

We project that XF-73 will receive regulatory approval followed by a launch in the US and Europe in 2028. Currently, decolonisation is largely achieved through use of the generic antibiotic mupirocin, so we expect it to take time for a novel product such as XF-73 to reach a large market share. We thus assume that a peak market share of 25% is reached in the US after 7 years. In Europe, which is a more conservative market, we assume a peak market share of 18% after 9 years.

Market exclusivity until late 2030s in the US

XF-73 has received the FDA's QIDP designation, which grants an additional 5 years of exclusivity on approval, following 5 years of NCE market exclusivity, extending protection until at least 2038 (assuming a 2028 launch). In addition, there are 3 tiers of patents which could extend protection further. We assume no revenues beyond 2038 in our model.

QIDP status highlights the potential for XF-73

The FDA's QIDP designation is designed to expedite the development and approval of new antibiotics and antifungals targeting serious or life-threatening infections, offering 5 years of additional market exclusivity and priority review to address the urgent need for effective treatments.

In 2015, the FDA awarded XF-73 nasal a Qualified Infectious Disease Product ("QIDP") designation (see margin) for the indication of prevention of post-surgical staphylococcal infections including MRSA. The QIDP status confers priority review and an additional 5 year extension of US market exclusivity when the product is approved. In 2019, XF-73 nasal was also awarded Fast Track designation by the FDA, which ensures frequent communications with and help from the FDA, which is likely to help Destiny achieve approval earlier than they otherwise would.

We anticipate a price of $250 in the US and $100 in Europe

We conducted a value-based pricing assessment in the US (below) which estimates that by utilising XF-73 in high-risk surgical patients, the healthcare system can save $1.9bn by preventing post-surgical *S. aureus* infection, which, in our view, easily justifies a price of $250 for each course of treatment. In Europe, we conservatively assume a 60% discount to the US price. Please note that these are net price forecasts and assume no net price growth between the launch and peak sales year. In practice, the list price will likely be ~20% higher than the net price

in year one, with the discount widening to c. 40% by peak sales year, offsetting list price increases.

Table 12: Value-based pricing estimates for XF-73

Parameters	Values
Number of surgeries in US (thousands)	22,500
Estimated post-surgical infection rate	0.75%
Of which percentage caused by S. aureus	*22%*
Of which percentage that are considered high-risk	*80%*
Number of *S. aureus* infections among high-risk patients (thousands)	**29.7**
Cost for patient treated with surgical infections	$100,000
Est. cost to US HC system of post-surgical *S. aureus* infections ($m)	**2,970**
Elimination efficacy of *S. aureus* by XF-73 (P2b results)	84% vs. 25% (SOC*)
Correlation between elimination of *S. aureus* and preventing infection	80%
Total healthcare saving ($m)	**1,860**
Value-based price for one course of XF-73 ($)**	**$250**

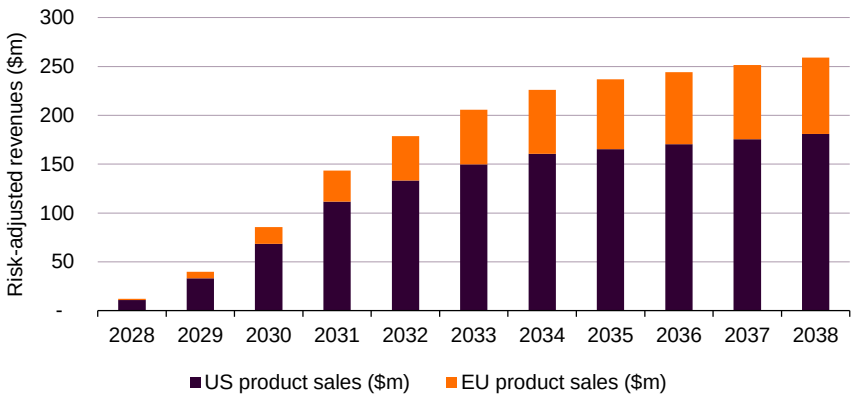
*Source: Intron Health estimates * SOC – standard of care ** Assumes 100% of high risk patients are treated*

- Our HC savings estimate does not account for the benefit of XF-73 completing nasal decolonisation in 24 hours (vs 5 days for mupirocin), which could reduce the number of hospital stay days
- Highly effective *S. aureus* decolonisation and prolonged protection would reduce horizontal transmission rate to other patients in the hospital, further reducing hospital spending

Risk-Adj. Peak Sales to Reach £185m in 2035

We apply a 30% risk adjustment to our sales forecast, which generously accounts for the clinical study and regulatory risk still present for XF-73, as well the risks around convincing payers to reimburse it in what is an unusual setting for new pharmaceutical products. It also accounts for the risks around find the right partner with whom to entrust the commercial launch. We forecast peak global sales (2035) of £185m (£620m non-risk adjusted). We show the revenues trajectory in the chart below, but it is important to note that we assume Destiny will out-license the rights to XF-73 in all geographies, so they will not book these revenues, instead receiving milestones and royalties.

Chart 5: Risk-adjusted global revenues for XF-73



Source: Intron Health estimates

Intensive care patients are universally decolonised (5-6m per year in the US) and dialysis patients are regularly decolonised

Upside potential with line extensions and sales from RoW

In addition to high-risk surgical patients, XF-73 has the potential for expansion into other patient cohorts, such as ICU or dialysis patients (see margin), if repeat administration is proven safe and effective. Furthermore, there is the possibility of using XF-73 for universal decolonisation in all surgeries, pending successful medical recommendations. Destiny estimates that these combined expansion opportunities could contribute an additional $1 billion in peak sales. Moreover, revenue from product sales in markets outside the US (RoW) may be realized following successful commercialisation efforts. We believe that for future indications, XF-73 may only need to show a positive readout on a microbiological, rather than a clinical, endpoint, which would reduce the time and cost to approval.

UK's NHS is expanding its antibiotic pilot scheme

As an example of the potential outside the US, the NHS has recently expanded its antibiotic pilot scheme to encourage the development of new anti-infective treatments. Under new rules, drugmakers would receive up to £20m/year for selling novel antibiotics in England, which is double the previous figure. The EU is also looking to incentivise anti-infectives, with proposals for a scheme to award an extra year of exclusivity (applied to any drug of their choice) for a company that gets approval for a new antibiotic.

NTCD-M3: Best-in-Class Prevention of rCDI

***C. difficile* infection (CDI) is caused by the proliferation of toxic *C. difficile* strains in the gut. It is treated with the use of antibiotics, which further disrupt the gut microbiome, resulting in a higher risk of recurrence. The available adjunct therapies (antibiotics, mAb, and FMT) are limited by their inadequate efficacy, safety concerns, inconvenient dosing and high costs. Recently approved FMTs have been associated with safety concerns and thus are only recommended for use following more than 2 CDI incidences. Destiny has developed a benign strain of *C. difficile*, NTCD-M3, which outcompetes pathogenic strains from causing infection. It provides protection during the crucial few weeks following antibiotic treatment before giving way to a restored gut microbiome. Comparing to FMTs, NTCD-M3 has demonstrated superior recurrence prevention (5% recurrence vs. 11% for VOWST), better tolerability, and potential to be used in earlier settings (after 1st CDI incidence vs after 2+ CDI incidences). In Feb 2023, Sebela acquired the US rights and will fund the P3 studies, reducing the development risk and we expect Destiny to also out-license the European rights in time. We forecast a potential launch in 2028 and non-risk adjusted peak sales of £280m by 2036 (£112m with 40% risk-adjustment), of which Destiny would be entitled to £18m in peak risk-adjusted royalty payments (in addition to potential milestones).**

NTCD-M3 is a Non-Toxigenic Strain of *C. difficile*

Recurrent *C. difficile* infections are a large unmet medical need today, with antibiotics remaining the standard of care, despite their use making future infections even more likely. Against this background, Destiny's NTCD-M3 is a naturally existing strain of *C. difficile* that does not possess the genes responsible for producing toxins, which cause the symptoms of *C. difficile* infection. Thus, it can proliferate in the colon and out-compete the pathogenic form of *C. difficile*, preventing a recurrence of the infection. The drug is administered in the form of spores to be taken orally following antibiotic therapy to deal with the original *C. difficile* infection. NTCD-M3 has been awarded Fast Track designation by the FDA.

A Unique Mechanism of Action

Most treatments for *C. difficile* involve destroying the pathogenic bacteria using antibiotics. While this is usually successful in achieving that goal, the antibiotics also destroy other bacteria lining the colon, which perform many essential functions in the body, including in digestion and immune function. This creates dysbiosis – an imbalance in gut microbiota – leaving the door wide open to another opportunistic infection by *C. difficile*. Although the antibiotics kill the bacteria, they do not kill its

spores, which remain in the colon and can germinate once the antibiotics have worn off. This creates a cycle of disease recurrence.

NTCD-M3 takes a fundamentally different approach. After completing antibiotic therapy to destroy the pathogenic *C. difficile* infection in the colon, NTCD-M3 is administered in the form of spores and germinates within the colon. This non-toxic strain of *C. difficile* colonises the colon, thriving in the microbiome-depleted gut environment. It out-competes and prevents growth of toxic *C. difficile* strains. NTCD-M3 is present in the gut for several weeks, providing protection during the few weeks of critical recovery period post-antibiotic treatment, giving some time for the microbiome to recover and prevent *C. difficile* reinfection.

Differentiated Profile Has Best-in-Class Potential

NTCD-M3 has demonstrated a differentiated profile and, in our view, best-in-class potential for preventing recurrent *C. difficile* infection (rCDI):

- A leading dataset vs other options approved or in development
  - P2b data showed NTCD-M3 was able to reduce the CDI recurrence rate by >80% (from 30% in the placebo arm to 5%)
- It is a once-daily, oral dose and has a fast onset of action
- The strong safety profile allows it to be used in combination with other therapies to offer greater protection, if necessary
- While other prophylactic options are generally considered in the second or third recurrence, NTCD-M3 is positioned as a 1L option for application following treatment of the first CDI
- It can potentially safeguard intestinal health during the critical recovery period following antibiotic therapy without causing long-term changes to the patient's microbiome, unlike FMT, which permanently changes it, with unknown long-term consequences

Destiny Acquired Rights to NTCD-M3 in 2020

In 2020, Destiny Pharma entered into an exclusive license agreement to obtain global rights (ex-China) to develop and commercialise NTCD-M3 from NTCD, LLC. As a part of the agreement, Destiny Pharma made an upfront payment of $3 million and has agreed to pay future milestones and undisclosed royalties on future revenue. The asset was developed by GI infection physician Professor Dale Gerding, who is a world-leading specialist in *C. diff*icile, with more than 400 peer-reviewed journal publications, book chapters and review articles in this space. Destiny took the asset through phase 2b trials, publishing positive data which they used to agree a phase 3 design through talks with the FDA and EMA.

Sebela Pharma to Fund Development in N. America

In February 2023, Destiny Pharma entered into an exclusive agreement with Sebela Pharmaceuticals to exclusively co-develop NTCD-M3 in North America (US, Canada, Mexico) for the prevention of rCDI. Sebela will lead and fund future clinical development, including the Phase 3 trial, and commercialisation efforts. Under the agreement, Sebela holds a minority interest over income generated outside of North America, based on the clinical studies it will fund. Destiny Pharma received an upfront payment of $1 million and is eligible to receive further success-based and revenue-based milestone payments worth up to $570m as well as tiered, double-digit royalties on all North American sales. Destiny Pharma will provide all the necessary NTCD-M3 product for clinical studies.

Recurrent *C. diff* Infections: An Unmet Medical Need

We explain below how the recurrent *C. difficile* medical setting is a serious, unmet medical need that requires new therapies to address. *C. difficile* infections can be life-threatening and are responsible for 15-30k deaths in the US each year. Recurrences are likely and become increasingly more likely with the more recurrences that occur. Antibiotics are effective at dealing with the immediate infection, but they also create the conditions that lead to the next recurrence, which usually manifests within a matter of weeks of the last infection. We also show that hypervirulent strains have made the problem more acute in recent decades, with both the frequency of recurrence increasing and the severity of disease.

Clostridioides difficile infection (CDI)

Often referred to as *C. difficile* or *C. diff*, *Clostridioides difficile* is a gram positive, anaerobic bacterium that causes colitis - infection of the large intestine. Outside the large intestine, it remains in a dormant state, allowing it to spread and survive for a long period of time and for asymptomatic carriers to spread infections. It becomes active when it enters the digestive system, causing a range of symptoms, which can range from mild to severe. These commonly include diarrhoea, fever, nausea and the presence of blood in the stool. In severe cases, CDI can be life-threatening and has a high hospital mortality rate of up to 25% in frail, elderly people. Each year in the US, 500k cases of *C. diff* are reported and 15-30k deaths in the US are associated with CDI. CDI has a significant economic impact on healthcare systems, with an annual cost exceeding $6 billion in the United States alone.

CDI is caused by disruption of the gut microbiome

Up to 2,000 species of bacteria and 100 trillion bacteria cells reside in the lining of a healthy intestine – this community of microbes play important roles in digestion and immune function and are collectively referred to as the gut microbiome. However, the use of antibiotics, and particularly

broad-spectrum antibiotics, can eliminate a majority of these healthy bacteria, significantly disrupting the gut microbial balance. This provides an opportunity for *C. diff* to proliferate, as it faces limited competition in the altered colon environment. The overgrowth and colonisation of *C. diff* leads to the release of toxins (known as toxin A and toxin B) in the intestine, resulting in infection, with symptoms usually manifesting within 5-10 days after starting a course of antibiotics, though they can emerge up to three months later.

Antibiotics are the standard of care, but also cause recurrence

Recurrent CDI (rCDI) is often defined as a second episode of CDI within 8 weeks of a previous episode; the rate of recurrence ranges from 15-35%.

Once CDI is suspected, current antibiotic use is discontinued and specific antibiotics that are known to be toxic to *C. diff* are instead prescribed. These include metronidazole, vancomycin or fidaxomicin. While usually effective at killing the *C. diff* infection, they also kill healthy bacteria and so the dysbiosis (imbalance in gut microbiome) remains. *C. diff* spores will remain in the colon, so once antibiotic use is discontinued, a recurrence of the *C. diff* infection is quite likely (see margin), making it an extremely challenging disease to treat over the long-term. Moreover, after one recurrence, the risk of further recurrences significantly increase. The recurrence rate is also higher for CDI acquired in hospitals and studies suggest that the recurrence rate has risen steeply in the past two decades.

- 25% of patients who have a first recurrence will experience a second
- 45% of patients who have a second recurrence will experience a third
- 60% of patients who have a third recurrence will experience a fourth

Emergence of hypervirulent strains has led to higher recurrence

Since 2013, there has been a notable increase in the incidence, virulence and resistance to treatment of CDI. This concerning trend is closely associated with the emergence of hypervirulent strains, notably the NAP1/BI/027 strain, which produces higher amount of toxins and are more prone to causing severe and recurrent CDI cases.

Recurrent CDI (rCDI) is very challenging to treat…

Treatment for rCDI involves 1) removing the current *C. diff* infection, and 2) restoring normal gut microbiota, so that the infection does not return. Whilst it is relatively easy to achieve the first step, restoring the gut microbiome is much harder, especially if the patient requires further antibiotics for other conditions. Typically, a first recurrence is treated with vancomycin 4x daily for ten days, or fidaxomicin 2x daily for 10 days. However, if a second recurrence occurs, then doctors increasingly prescribe a faecal microbiota transplant (FMT), where faecal matter from a healthy donor is transplanted into the diseased colon. The theory behind this is that the healthy faecal matter will contain a diverse and balanced microbe community that will restore the microbiome in the rCDI

patient, preventing a third (or later) relapse. Cure rates with FMT are high, ranging from 70-90% depending on the setting. However, there are some downsides to FMT treatment, as we discuss later in the note.

FMT is Changing Landscape, But Still Has Problems

Prophylaxis therapy can be effective in preventing rCDI. Of the three approved treatment options that currently exist, the antibody Zinplava has a limited efficacy profile, in our view, which likely arises from it only targeting one of the two toxins that *C. difficile* produces. The other two options are both faecal microbial transplants (FMT), which have greater efficacy, though as we explain, they also come with their own drawbacks. In the table below, we have included efficacy data from the labels, though it is important to note that the study designs were materially different, so cross-trial comparisons should be done cautiously.

Table 13: Recently approved therapies for the prevention of rCDI by the FDA

Drug	Company	Molecule	Year approved	Mechanism of action	Delivery Mechanism	Recurrence rates	Indication
ZINPLAVA	Merck	Bezlotoxumab	2016	Monoclonal antibody that binds to and inhibits toxin B	Single dose of IV	Week 12* ZINPLAVA: 16.6% Placebo: 26.7%	Reduce recurrence of CDI in adults and children older than 1 who are receiving antibacterial drug treatment of CDI and are at a high risk for CDI recurrence.
REBYOTA	Ferring	Faecal microbiota	2022	Restores gut microbiota diversity	Single dose rectal administration	Week 8 REBYOTA: 29.4% Placebo: 42.5%	For the prevention of recurrence of CDI in adults following antibiotic treatment for recurrent CDI.
VOWST	SERES	Faecal microbiota	2023	Restores gut microbiota diversity	4x daily pill for three days	Week 8 Vowst: 12% Placebo: 40%	For the prevention of recurrence of CDI in adults following antibiotic treatment for recurrent CDI.

*Source: FDA, Intron Health estimates * Average results from the two Phase 3 studies*

FMT now available in pill form; previously required colonoscopy

Prior to 2022, when the first FMT enema, Rebyota, was approved, FMT therapy generally required a colonoscopy to transfer the faecal matter, which is an invasive and expensive procedure, limiting the number of patients who underwent treatment. Moreover, faecal donors had to be found on an *ad hoc* basis, which also reduced the practicality and consistency of treatment. As of April 2023 however, there are now two standardised options in the US – Rebyota (enema) and Vowst (oral, though requires laxatives to be taken before administration). Vowst has strong data, reducing the rate of rCDI by 68% vs placebo at 8 weeks and by 54% at 12 weeks. We expect FMT use to increase with this safer, less invasive option.

….But rCDI guidelines are yet to fully reflect new FMT treatments

The American College of Gastroenterology treatment guidelines recommend that FMT is only used after a second recurrence, but they were last updated in 2021 and we believe they could be updated at a later date to factor in the new, more convenient FMT treatments. This being the case, we are likely to see the standard of care shift from the older antibiotics to the FMT treatments in the recurrent setting.

But FMT still has many uncertainties which may curtail its use

While there is clearly a strong rationale to use FMT in patients with rCDI, there are also some potential risks. Most notably, this includes the risk of infection transmission, even if viral screens are used (there have been reported cases of lethal pathogen infections in the past, which has greatly concerned the FDA). As new diseases such as Mpox emerge, it also necessitates the need for screen to be constantly updated. It has been suggested that certain metabolic states, such as being more prone to obesity, could also be transferred from the donor to the patient and there is strong evidence from animal studies that suggests this could be the case. The gut microbiome is also intimately connected to neurological diseases, such as depression, but this link is poorly understood. Fundamentally, our knowledge of the gut microbiome or its complex interactions with the immune system and brain is at a very early stage, so transplanting the microbiome of another human into someone else could have unexpected consequences.

Microbiome therapies may be still 5 years away in Europe

The development of microbiome-based treatments in Europe are significantly behind the US, with no approved therapies or established regulatory pathways. Although some European countries have regulations for FMT, there is a lack of EU-wide guidance. However, it is anticipated that marketing authorisation submissions for FMT may occur within the next 5-10 years, as indicated in the EMA report from June 2022. Companies such as Destiny Pharma and Ferring are actively working with regulatory agencies to establish a pathway and align on trial designs.

Phase 2 Data Showed 72% Risk Reduction of rCDI

Among 173 patients with a first episode or first recurrence of CDI in a phase 2 study, NCTD-M3 treatment (across all doses, following antibiotics to treat the initial infection) decreased the rate of infection recurrence by 72% at 6 weeks and this reached a high level of statistical significance. Looking into the individual dosing groups, which were relatively small (N=~42), the high dose group who received NCTD-M3 for 7 days had a 90% lower risk of a recurrence within 6 weeks, which was also statistically significant. The other doses both achieved a 60% decline in the risk of recurrence, but these were not significant due to the small size of the arms and the study was never intended to be powered to show significance for each dose.

Table 14: Phase 2 trial efficacy results

Trial Design	**Phase 2, randomised double-blind**			
Patients	Patients with CDI. First episode or first recurrence and treated with antibiotics (metronidazole, vancomycin or both)			
rCDI endpoint	**NCTD-M3 (N=125)**	**Placebo (N=43)**	**Risk reduction**	**Significance**
Rate of recurrence within 6 weeks	11%	30%	**72%**	**P=0.006**
	High dose* for 7 days (N=43)			
	5%	30%	**90%**	**P=0.01**
	High dose* for 14 days (N=41)			
	15%	30%	60%	P=0.10
	Low dose** for 7 days (N=41)			
	15%	30%	60%	P=0.11

*Source: Company Reports * 10^7 spores/day ** 10^4 spores/day*

- CDI recurrence was only 2% in those patients who were confirmed as having their colon colonised by NTCD-M3, vs 31% in those whose colons had been colonised
  - This is strong evidence, in our view, that efficacy is being driven by NTCD-M3 out-competing pathogenic *C. diff*, as per the hypothesis
- Competitor prophylactic drugs saw relapse rates of 12-30% at 8-12 weeks, which suggests to us that NTCD-M3 has the potential to build a best-in-class efficacy profile at phase 3

Rapid colonisation is unaffected by simultaneous antibiotic use

Following the ingestion of NTCD-M3 spores, stool cultures have revealed high rates of colonisation, with 71% of patients receiving 10^7 spores/day having detectable levels of NTCD-M3 bacteria in stools. Additionally, in those that received simultaneous antibiotics (N=25), there was not reduced NTCD colonisation, with 84% of patients having colonisation occur, vs 65% when antibiotics were not applied. This is encouraging, as since the end of the study, a new antibiotic called fidaxomicin was added to US clinical guidelines for treating CDI, and it is known to reside for a longer period in the gut than other CDI antibiotics. These results suggest that NTCD-M3 colonisation would not be affected by such use.

NCTD-M3 was found to be well tolerated and safe

Most adverse events were gastrointestinal, occurring at lower incidence than placebo. The treatment emergent and serious adverse event rate was 78% and 3% for NCTD-M3, vs 86% and 7% for placebo respectively.

Table 15: Phase 2 safety data

Safety	**NCTD-M3**	**Placebo**
Treatment emergent adverse events	78%	86%
Serious treatment emergent adverse events	3%	7%
Discontinuation due to AE	3%	7%
Deaths	1%	2%
Most frequent AEs:		
Diarrhoea	46%	60%
Abdominal pain	17%	33%
Flatulence	17%	16%
Headache	10%	2%
Nausea	7%	7%

Source: JAMA 2015

No potential for toxic gene transfer from pathogenic bacteria

An *in vitro* study successfully showed that there is no potential for the transfer of the gene responsible for toxin production from a pathogenic strain of *C. difficile* to NTCD-M3. In the study, attempted conjugations using a pathogenic *C. difficile* strain (630Δerm) as a gene donor failed to show toxin gene transfer to NTCD-M3, but did infect another non-toxic CD37 strain under the same conditions. This data is important, as such a gene transfer would have enabled NTCD-M3 to manufacture the toxins produced by pathogenic *C. difficile*, which are responsible for causing major life-threatening symptoms.

Phase 3 Study to Begin in 2024

Destiny Pharma is working with its partner Sebela to prepare for a pivotal Phase 3 study to start in 2024. They have held a Type C meeting with the FDA and also engaged with the EMA. Both these agencies have agreed to the design, endpoints and enrolment size for a single phase 3 study which will be acceptable for a regulatory filing.

Table 16: Trial design for a pivotal Phase 3 study

Factor	
Trial design	Randomized, double-blind, placebo-controlled
Indication	Prevention for recurrent CDI following antibiotic therapy
Recruitment size	700
Randomization	2 : 1 (Treatment vs Placebo)
Estimated trial start	2024
Estimated trial completion	2026

Source: Company reports

Competitive Landscape is Favourable to Destiny

The next generation of microbiome-altering therapeutics, as we have discussed, come with a number of potential downsides and uncertainties. Vedanta's VE303 is a more controlled and scalable FMT-like product, being manufactured from a cell-bank, and its Phase 2 data looked comparable to FMT but inferior to NTCD-M3. In our view, producing VE303 at scale may be a challenging process, with likely 10x the cost of NTCD-M3. In addition, there seems have been a delay to its Ph3 programme, which is rarely a positive development, especially given the high risk of the programme. The only other innovative product is Lumen's LMN-201, which is a microbe-based therapy which seeks to degrade *C. diff* and inhibit the toxin B that it produces. However, we have yet to see proof-of-concept data and so it remains an unproven therapy and some way behind Destiny's NTCD-M3.

Table 17: Competitive Landscape for the prevention of recurrent CDI

Asset	Company	Development Stage	Mechanism	Administration	Dosing Regimen
ZINPLAVA	Merck	Approved	mAb that binds to and inhibits toxin B	IV	Single dose
REBYOTA	Ferring	Approved	Restores gut microbiota diversity (FMT)	Enema	Single dose
VOWST	SERES	Approved	Restores gut microbiota diversity (FMT)	Oral	4x daily for 3 days
VE303	Vedanta Biosciences	Ph3 planned for 2023	Cell-bank derived microbes to restore gut microbiota	Oral	Ten capsules daily for 14 days
Destiny Pharma	**NTCD-M3**	**Ph3 planned for 2024**	**Non-toxic strain of *C. diff***	**Oral**	**4x daily for 7 days**
Lumen Bioscience	LMN-201	Ph2 ongoing	Engineered strains of spirulina bacteria to degrade cell wall of *C. diff* and inhibits toxin B through target binding	Oral	Unknown
Finch Therapeutics	CP101	Ph3 discontinued in Jan-23 for non-clinical reasons*	Microbes from healthy donors (FMT)	Oral	Single dose
Pfizer	New *C. diff* Vaccine	Ph1/2 ongoing	Prophylactic vaccine for healthy individuals	Intra-muscular injection	2 doses given 2 or 6 months apart

Source: Company reports; Intron Health estimates
** This FMT study had to be discontinued due to corporate finance issues; given the current landscape we believe it is unlikely to be picked up and further developed*

- VE303 consists of consortium of 8 bacteria produced from a pure, clonal cell-bank, instead of derived from donor faecal material. Compared to FMTs, VE303 is manufactured from a scalable process with a higher product consistency.
  - However, it only achieved a ~13% recurrence rate in its phase 2 trial, vs 5% for M3
  - Moreover, the lower dose arm did not meet statistical significance on recurrence rate vs placebo
  - It also has a more burdensome treatment regimen vs M3
  - Commencement of its Phase 3 program appears to have been delayed from 2022 to 2024
- Following poor efficacy reported for Pfizer's prophylaxis vaccine for CDI in a P3 trial, Pfizer has started investigating new formulations in its Ph1/2 trial
  - Even if successful, this product remains at an early stage of development and is targeting a different market to NTCD-M3

Risk-Adj. Peak Sales to Reach ~£112m by 2036

We show below that the risk adjusted sales for NTCD-M3 can reach £112m by 2036 (£281m in non-risk adjusted sales). The approval of FMTs since 2022 is shifting the treatment landscape; however, they are expensive, only approved for use in the rCDI setting, and are associated with safety concerns. We believe NTCD-M3 has a superior profile, which positions it so that it could capture 40% peak market share in the rCDI setting. Furthermore, we expect it to gain approval for use after a primary CDI incidence, not just in the recurrent setting. We anticipate a price at $4,500 in the US and $2,000 in Europe, which is similar to antibiotics and will help NTCD-M3 to build out the primary CDI market and outcompete FMTs in rCDI with its superior profile. Following the successful deal with

Sebela to out-license US rights, we expect Destiny to also seek a partner to purchase the European rights.

Table 18: NTCD-M3 global revenues forecast

£m	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040
US													
TAM	8,861	11,163	15,792	24,856	34,182	45,819	57,444	64,174	67,009	67,679	68,356	69,040	69,730
Market share	13%	28%	41%	54%	62%	68%	72%	74%	74%	71%	67%	63%	60%
Patients treated	1,156	3,152	6,471	13,484	21,028	31,083	41,259	47,211	49,658	47,846	45,776	43,660	41,496
Price ($/course)	4,968	5,068	5,169	5,272	5,378	5,485	5,595	5,707	5,821	5,938	6,056	6,178	6,301
Sales (£m)	4.5	12.5	26.1	55.5	88.4	133.2	180.4	210.5	225.8	221.9	216.6	210.7	204.3
Risk-adjusted sales	**1.8**	**5.0**	**10.5**	**22.2**	**35.3**	**53.3**	**72.1**	**84.2**	**90.3**	**88.8**	**86.6**	**84.3**	**81.7**
growth		*178%*	*109%*	*113%*	*59%*	*51%*	*35%*	*17%*	*7%*	*-2%*	*-2%*	*-3%*	*-3%*
Europe													
TAM	8,861	11,163	15,792	24,856	34,182	45,819	57,444	64,174	67,009	67,679	68,356	69,040	69,730
Market share	5%	8%	13%	29%	38%	44%	49%	52%	53%	53%	53%	53%	53%
Patients treated	443	893	2,053	7,208	12,989	20,160	28,148	33,370	35,515	35,870	36,229	36,591	36,957
Price ($/course)	1,987	1,987	1,987	1,987	1,987	1,987	1,987	1,987	1,987	1,987	1,987	1,987	1,987
Sales (£m)	0.7	1.4	3.2	11.2	20.2	31.3	43.7	51.8	55.1	55.7	56.2	56.8	57.4
Risk-adjusted sales	**0.3**	**0.6**	**1.3**	**4.5**	**8.1**	**12.5**	**17.5**	**20.7**	**22.1**	**22.3**	**22.5**	**22.7**	**23.0**
growth		*102%*	*130%*	*251%*	*80%*	*55%*	*40%*	*19%*	*6%*	*1%*	*1%*	*1%*	*1%*
US + Europe													
Risk adjusted sales (£m)	2	6	12	27	43	66	90	105	112	111	109	107	105
Royalties to Destiny (£m)	**0**	**1**	**1**	**3**	**6**	**9**	**14**	**16**	**18**	**17**	**17**	**17**	**16**

Source: Intron Health estimates

TAM is growing fast, reaching ~38k in the US and Europe by 2035

In 2022, there were ~500k cases of CDI among adults in the US. Out of these, we estimate 398k are primary CDI incidences, 72k are first CDI recurrence, and 31k are subsequent recurrent cases, based on the recurrence rates shown below. We project that the primary CDI incidence will grow by 1% each year because of an ageing population and increased use of antibiotics. The recurrence rate following primary CDI incidence is expected to remain stable at 18%, in our view. The utilisation of adjunct therapies (e.g. NTCD-M3, FMT, etc.) following antibiotic treatment increases following each CDI recurrence. As more effective treatment options are utilised, we expect a modest decline in recurrence rate over time.

Table 19: CDI incidence and addressable cases in the US

£m	2028	2029	2030	2031	2032	2033	2034	2035	2036
Total CDI incidence	530,076	535,147	540,266	545,434	550,572	555,758	560,993	566,603	572,269
Primary CDI	**422,109**	**426,330**	**430,594**	**434,900**	**439,248**	**443,641**	**448,077**	**452,558**	**457,084**
Of which treated	*337,687*	*341,064*	*344,475*	*347,920*	*351,399*	*354,913*	*358,462*	*362,047*	365,667
Receiving adjunct therapy after antibiotics	**338**	**1,023**	**3,100**	**8,698**	**15,813**	**25,909**	**36,563**	**43,084**	**45,708**
As %	*0.1%*	*0.3%*	*0.9%*	*2.5%*	*4.5%*	*7.3%*	*10.2%*	*11.9%*	12.5%
1st Recurrence	**75,980**	**76,739**	**77,507**	**78,282**	**79,065**	**79,855**	**80,654**	**81,460**	**82,275**
Of which treated	72,181	72,902	73,632	74,368	75,111	75,863	76,621	77,387	78,161
Receiving adjunct therapy after antibiotics	**3,248**	**4,228**	**5,891**	**8,180**	**9,764**	**10,772**	**11,493**	**11,608**	**11,724**
As %	*5%*	*6%*	*8%*	*11%*	*13%*	*14%*	*15%*	*15%*	15%
Subsequent recurrences	**31,987**	**32,077**	**32,165**	**32,252**	**32,258**	**32,262**	**32,262**	**32,584**	**32,910**
Of which treated	31,028	31,115	31,200	31,285	31,291	31,294	31,294	31,607	31,923
Receiving adjunct therapy after antibiotics	**5,275**	**5,912**	**6,802**	**7,978**	**8,605**	**9,138**	**9,388**	**9,482**	**9,577**
As %	*17%*	*19%*	*22%*	*26%*	*28%*	*29%*	*30%*	*30%*	30%
Total patients receiving adjunct therapy	**8,861**	**11,163**	**15,792**	**24,856**	**34,182**	**45,819**	**57,444**	**64,174**	**67,009**

Source: Intron Health estimates

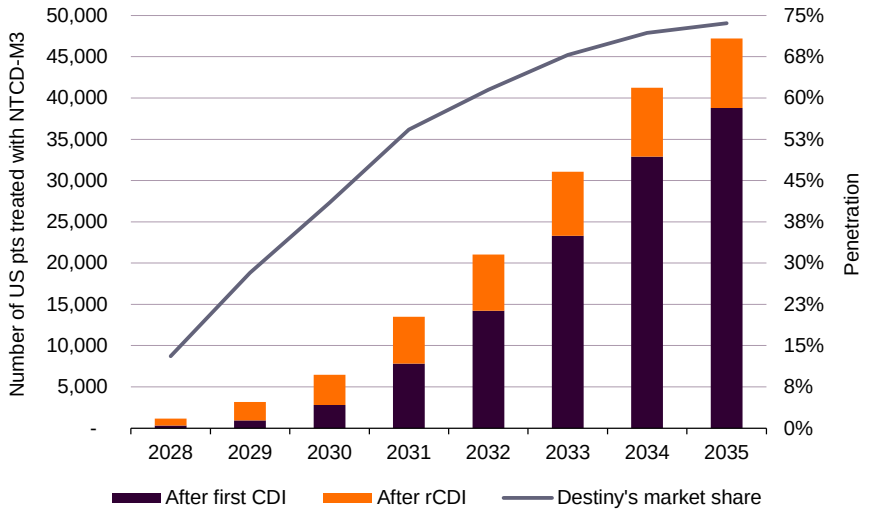
- We expect the CDI treatment rate will remain steady for each setting:

  - Primary incidence (1st case): 80%, based on US CDC data
  - 1st recurrence: 90%
  - Subsequent recurrences: 97%
- Estimated baseline recurrence rates across CDI types: 26%
  - Primary incidence: 18%
  - 1st recurrence: 25%
  - 2nd recurrence: 45%
  - 3rd recurrence and beyond: 60%
- We estimated the percentage of patients receiving adjunct therapy following antibiotics for the prevention of CDI recurrence
  - Primary incidence: 0% in 2027, growing to 12.5% beyond 2036 following the approval of NTCD-M3 in this setting
  - 1st recurrence: 3% in 2023 (Intron estimates), growing to 15% beyond 2034 due to off-label use and potential approvals
  - 2nd recurrence and beyond: 15% in '23, growing to 30% beyond '34

We assume a 2028 launch and peak market share of 63% in the US

We expect Sebela to initiate pivotal Phase 3 studies in 2024, with a readout likely by H2 2026. We assume an FDA approval and launch in the US in early 2028 for prevention recurrence after the primary CDI or rCDI incidence. With a potential best-in-class profile, we expect NTCD-M3 will steadily gain market share while benefitting from an expanding treatment rate, achieving a peak market share of 74% in 2036 (90% share in 1st CDI setting, 40% in the recurrent CDI setting), 8 years after launch.

Chart 6: US patients treated with NTCD-M3 and its market share



Source: Intron Health estimates

- Following primary CDI, we expect NTCD-M3 to be the only other approved option besides Zinplava, which has been poorly utilised due to limited efficacy. We expect NTCD-M3 will capture 90% of the market share in this setting and materially improve the treatment rate.
- In the rCDI setting, we expect NTCD-M3 to be competitive despite competition from FMT and upcoming therapies such as VE303. Based on its superior safety and efficacy profile, we expect NTCD-M3 to secure a peak market share of 40%
- We assume other innovative options may become available beyond 2037, leading to a slight decline in market share for NTCD-M3

Market exclusivity expected until 2040 in the US

Based on our forecast of an FDA approval and launch in H1 2028, we expect NTCD0M3 will be protected until 2040 with 12 years of biologics marketing exclusivity.

Competitive pricing to reflect superior product profile

Based on the price of approved treatment options, we forecast NTCD-M3 will be priced at $4,500 and $2,000 for a course of treatment in the US and Europe, respectively. We expect it to be priced similarly to the antibiotic treatment fidaxomicin, facilitating the development of an adjunct therapy market following primary CDI. This price allows further differentiation from FMT besides its superior profile in the rCDI setting. We assume that the price will increase annually by 2% in the US while remaining unchanged in Europe. We note that the final product price will be set by Sebela in the US.

A few price benchmarks for consideration:

- Vowst carries a list price of $17,500 in the US, which has a similar net price to NTCD-M3 at a 30% discount. However, it is only approved in the rCDI setting, with numerically inferior protection compared to NTCD-M3.
- Rebyota carries a list price of $9,500, but we believe its use will be limited by its enema administration and lower efficacy.
- Antibiotic fidaxomicin carries a list price of $4,960 for a course of treatment for CDI, and we expect NTCD-M3 will be priced similarly on a net price basis

Penetration peak in a less developed European market in 2036

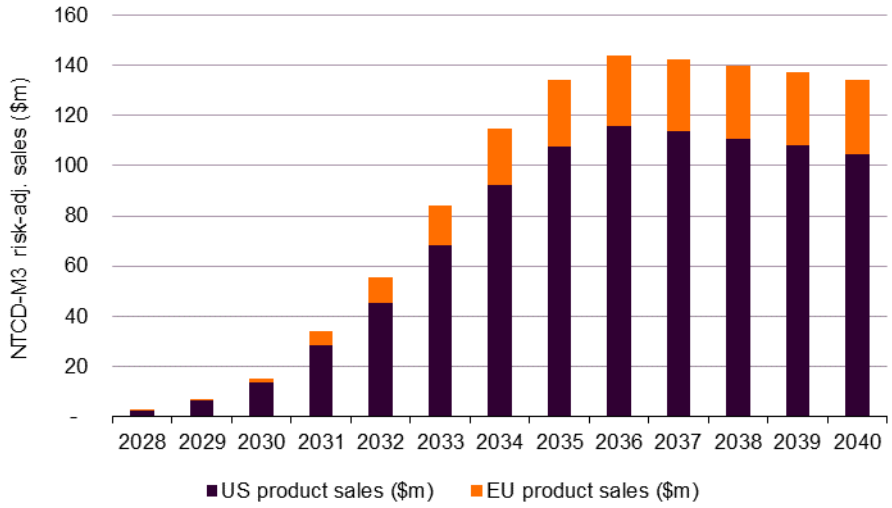
In Europe, we have assumed that the number of CDI cases mirrors that of the US. Since the EMA has not yet approved FMT, it is likely that NTCD-M3 will face less competition upon launch in the European market. However, due to the decentralised nature of market access in Europe,

we anticipate it will take 9 years to reach peak penetration, which we conservatively estimate at 53%.

Peak sales in the US+EU to reach £281m in 2036

We forecast that global peak sales will reach £281m in 2036 (£112m risk adjusted, assuming a 40% risk adjustment), which accounts for the Phase 3 clinical and regulatory development risk for NTCD-M3. We have a less severe risk adjustment for this asset compared to XF-73 as it has the validation that comes with a large out-licensing deal as well as more clinically relevant data from the phase II dataset. Commercially, the market is also better established for new entrants (i.e. FMTs are already penetrating the market) compared to XF-73's decolonisation regimen, which has used generic antibiotics for decades. The revenue trajectory for NTCD-M3 in US and Europe is shown in the chart below. However, we expect Destiny will out-license the rights in Europe, so they will likely receive an upfront, potential milestones and royalties on net sales instead of booking product revenues.

Chart 7: NTCD-M3 risk-adjusted product revenues from the US and Europe



Source: Intron Health estimates

Upside potential from RoW and indication expansion

With the superior safety profile, NTCD-M3 has the potential to expand into primary prevention for CDI among high-risk patients. According to Destiny, it has the potential to be used in elderly patients that have been admitted to hospitals or are on broad spectrum antibiotics, which could bring in an additional $300m peak sales from the US. Additional revenue may also be realised from international markets when NTCD-M3 is commercialised by Destiny directly or via a partner.

Early Pipeline Assets

XF-73 Dermal to Treat Skin Infections

Destiny have designed a novel formulation of XF-73 ("XF-73 Dermal") to be used for the treatment of antibiotic-resistant serious skin infections associated with open wounds or broken skin, such as burns and diabetic foot ulcers. A clinically-enabling study is expected to begin in 2023. China Medical Systems Holdings holds rights to develop XF-73 in the China region and is separately developing it for the prevention and treatment of superficial skin bacterial infections. Considering its early development status, we do not yet assign any value to this asset. However, we do expect to see some *in vivo* tox data by the end of the Summer.

Diabetic Foot Ulcers are the most common cause of amputation

Diabetic foot ulcers (DFU) are open wounds or sores on the skin that result from poor glycaemic control, underlying neuropathy and peripheral vascular disease. They are one of the most common causes of lower extremity amputation in diabetic patients and are responsible for more admissions than any other diabetic complication. It is estimated that 25% of US diabetic patients will suffer from a DFU in their lifetime and approximately 13% have active ulcers.

Infection leads to complications and increase risk of amputation

Infections may arise from inadequately managed DFU which can lead to further complications, including the risk of amputation. There is currently a lack of effective solutions for treating DFU or preventing infections.

XF-73 is an effective dermal option to prevent DFU infection

XF-73 Dermal is expected to be a rapid, cost-effective dermal treatment that kills all relevant bacteria in DFU quickly, helping the wound heal and reducing the threat of AMR through its novel, patented action.

Potential to expand into multiple indications

Destiny Pharma plan to develop XF-73 Dermal initially as a dermal therapeutic for the prevention/treatment of infections associated with DFU. The data generated in this programme will support the use case in multiple indications including impetigo, acne, atopic dermatitis, bacterial infected skin lacerations, candida skin/vaginal infections and the treatment of bacterial burn wound infections.

Encouraging efficacy with limited safety risk from preclinical data

XF-73 Dermal has displayed promising preclinical activity, with *in vivo* efficacy shown in multiple porcine and murine models of superficial skin and full thickness wound infection. *In vivo* safety results have demonstrated minimal systemic exposure and indicate a superior safety

profile. Destiny Pharma also has data supporting the efficacy in serious bacterial burn wound infection models in studies conducted in association with the US Department of Defence.

Clinical studies may initiate in 2024

Destiny Pharma will continue to work with NIAID to complete the preclinical safety package to support future clinical development of XF-73 Dermal in serious wound infections. A clinically-enabling GLP study (c.£800k funding from NIAID) is underway.

CMS leading development in China

Destiny Pharma's China regional partner, China Medical Systems Holdings (CMS) has established a dermal program with XF-73 for superficial skin infections of antibiotic resistant bacteria. The CMS is leading and undertaking this work at their own cost.

SPOR-COV for COVID and Influenza

SPOR-COV was developed for the prevention of respiratory infections such as COVID-19 and influenza. It functions via a distinct bacteria-based mechanism to stimulate the innate immune system. Compared to traditional vaccines, it has the potential advantage of having a faster onset of action, is effective against new viral variants and can be manufactured and scaled at a low cost. Preclinical data has demonstrated encouraging efficacy against COVID-19 and influenza. A Phase 1 study completed by Destiny's partner, HURO, supports the product's safety profile. Destiny are currently trying to determine the most value-creative path forwards, so we do not assign any value to this programme at present.

A nasal spray protecting against respiratory viral infections

SPOR-COV, a collaboration between Destiny Pharma and SporeGen (leading Bacillus experts), is a prophylactic nasal spray therapy for COVID-19, influenza and potentially all respiratory viral infections. It is composed of a proprietary formulation of *Bacillus* bacteria that gives the innate immune system the potential to develop protection after a few days of treatment. It has the potential to offer protection as a monotherapy or used in combination with vaccine therapies.

A distinct mechanism that differs from traditional vaccines

SPOR-COV stimulates various components of the immune system pathway. It uses the innate immune system to rapidly develop protection against COVID-19 and influenza within a few days of dosing. Additionally, the product, unlike traditional vaccination, has been shown not to be impaired by new mutational variants. The product is stable and can

therefore be stockpiled indefinitely without the need for cold chain logistics.

Promising preclinical efficacy against COVID-19 and influenza

SPORCOV has been evaluated in several preclinical studies which have showed that it provides:

- Prophylaxis of COVID-19 in SARS-CoV-2 preclinical challenge models
- Significant reduction of signs and symptoms of influenza in multiple preclinical models. It has already been shown by SporeGen to provide complete protection vs influenza in pre-clinical models
- Potential as an adjunct/booster to existing vaccines, as backed by preliminary immunological research

Manufacturing and licensing agreement with HURO for Vietnam

Destiny Pharma signed a manufacturing and regional licensing agreement with HURO Biotech JSC for Vietnam. HURO is an experienced manufacturer of bacterial product formulations in Vietnam and is part of the PAN group. Under the terms of the strategic agreement, HURO has non-exclusive rights to supply future SPOR-COV supplies and also have exclusive rights to commercialise SPOR-COV in Vietnam. In return, HURO is developing manufacturing processes according to GMP-WHO standards and conducting other research, including human clinical tolerability studies, which will be shared with Destiny Pharma and SporeGen. The Phase 1 clinical studies have been completed successfully in Vietnam, with toxicology studies supporting its safety profile.

Seeking partners to advance the program in EU and US

Destiny are continuing to review the data generated from the grant funded collaboration and are planning the next steps for the programme, which includes the first human studies in Europe and the US. They are seeking additional partners to collaborate on the development and commercialisation of SPOR-COV outside Vietnam.

Funded Through to H2 2024

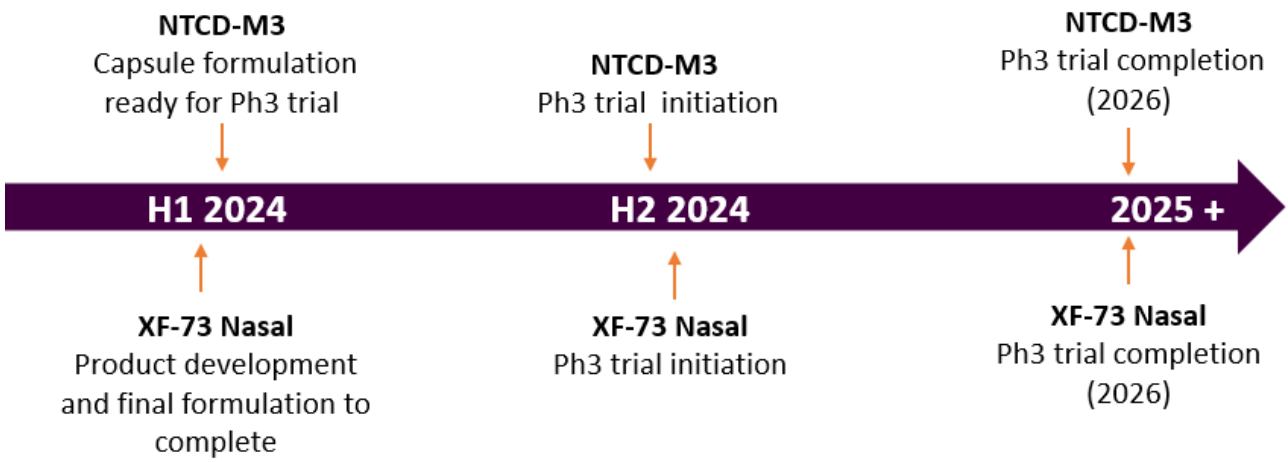
Destiny's financials are in a solid state, having carried out a fundraising in March 2023, which extended the runway into H2 2024. Moreover, the deal they signed with Sebela ensured that the phase III development costs of NTCD-M3 would be met by their partner, not by them. Thus, Destiny's operational costs are expected to be minimal – just ~£4-5m of G&A annually and early-stage R&D of around £3.5m (which we grow to £6m by 2028). We calculate an annual cash burn of £6-7m, so with £5m of cash at end 2022, and a £7m raise in 2023, we can attest that H2 2024 is a reasonable expectation of current runway. However, with the company's preferred strategy being very much to out-license their assets in all geographies, we expect this runway to extend following further out-licensing deals for XF-73 (globally) and/or NTCD-M3 (outside North America). Unlike with the Sebela deal, we would anticipate a future deal to include a very material upfront that would meaningfully extend runway, leaving the door open to Destiny to investing more strongly into its AMR pipeline to fulfil its ambition of becoming an AMR powerhouse. However, we do not currently include any upfronts in our base case forecasting given the uncertainty in timing and amount.

Oncology-Like Margins Expected

Both of Destiny's main products are expected to have very low COGS when compared to their pricing. In our view, COGS is likely to fall under 5% of sales. Combined with a low need for S&M costs, given the specialty care nature of the products (they are both hospital-only drugs, not likely to be dispensed by GPs/family physicians), we conclude that a commercial partner will find that the margins are oncology-like. Given this reality, we expect that Destiny will be able to negotiate favourable terms on any future deals, which are likely to include a material upfront, potential milestones in the hundreds of millions and royalties in the double digits, in our view. Such an income stream would make Destiny a very profitable company indeed, given their low opex burden.

Upcoming Catalysts

Chart 8: Expected Catalysts for Destiny Pharma



Source: Intron Health estimates, based on company reports

- NTCD-M3 – Complete manufacturing technology transfer to Sebela in 2023; Ph3 to start in 2024
- XF-73 – Secure commercial partner to co-develop asset
  - Product development and final formulation ongoing to produce gel for Ph3, complete by end of 2023
- XF-73 Dermal – Clinically-enabling GLP study to complete in 2023

Valuation Support TP of £1.20/Share

We have valued Destiny Pharma using a sum-of-the-parts which only accounts for NTCD-M3 and XF-73 and deducts NPVs for corporate G&A and R&D to 2028 (which would be easily sufficient to conclude those two main assets). Using the terms of the Sebela deal on NTCD-M3, we value it as being worth 50p/share to Destiny and we calculate that a similar deal struck for Europe would be worth another 19p/share. For XF-73, we believe that signing a development & commercialisation deal will be more challenging given 1) Potential partners need to be convinced of its unique profile and value proposition in a landscape littered with antibiotic failures, and 2) Pricing and commercial potential come with a large degree of uncertainty given the lack of precedents. Thus, we apply the lower risk adjustment of 30% and value the drug as currently being worth 86p/share to Destiny in this pre-deal stage of asset development. However, this leaves open the potential for a large valuation upgrade when a deal is signed, as we would have greater development and commercialisation visibility and would be able to reduce the magnitude of the risk adjustment and potentially increase our penetration assumptions. Deducting the corporate cost NPVs from the asset NPVs, we arrive at our current target price of £1.20/share.

Table 20: Destiny Pharma – SOTP valuation

	NPV ($m)	NPV (£m)	NPV (£/share)
NTCD-M3 (EU)	23.4	18.3	0.19
NTCD-M3 US (Sebela deal)	61.0	47.7	0.50
XF-73 (Out-licensed deal)	106.2	82.9	0.86
G&A to 2028	-25.1	-19.6	-0.20
R&D to 2028	-23.6	-18.4	-0.19
Net cash (2023)	7.9	6.2	0.06
Total	**149.8**	**117.0**	**1.22**
Target price			**1.20**
Market Cap	65.5	51.2	0.54
Upside			**2.3x**

Source: Intron Health estimates

Assumptions used in our valuation include:

- All assets are out-licensed in all regions from phase III, with the partner paying for all development and commercialisation costs; Destiny receives an upfront, potential milestones and royalties
- We use risk adjustments of 30% for XF-73 and 40% for NTCD-M3 to account for clinical, regulatory and partnering risk
- We assign no value to the XF platform, even though it is likely to produce more anti-microbial candidates in the future
- Because of their early nature, we do not assign value to other programmes in the pipeline
- We use a WACC of 11% and assume a tax rate of 20%
- We forecast G&A growing at 5% p.a. and R&D at 10% p.a. from 2023

There is a high potential for future valuation upgrades

- On any deal being signed, there is the potential for an upgrade if our deal assumptions prove to be conservative
- We can also reduce the partnering risk adjustment for XF-73 if a deal is signed with reasonable terms
- Clinical trial readouts, if positive, will result in a reduction to our clinical risk adjustments as well as potentially leading to increased penetration assumptions if the data is strong
- We have assumed zero sales outside of the US and Europe for both assets, so any sales or deals signed for these regions would represent pure upside to our valuation
- NTCD-M3 has indication expansion potential (e.g. into primary prevention), as does XF-73 (e.g. ICU and other high risk patients, such as CKD patients)
- Due to the high unmet need in nasal decolonisation, there may be material off-label uses for XF-73 in other indications

Company Background

Destiny Pharma is a clinical-stage biotechnology company focused on the development of therapeutics for infectious diseases, and in particular, antibiotic resistant bacteria. The most advanced assets include its lead product NTCD-M3 for *Clostridium difficile* infection recurrence and XF-73 for post-surgical *staphylococcal* hospital infections. The company is also co-developing SPOR-COV for the prevention of COVID-19 and influenza and an in-house XF-73 Dermal programme targeting wound and skin infections. Destiny was founded in 1997 by Dr William Love and conducted its IPO in September 2017.

Board and Management

Christ Tovey - CEO

Chris Tovey is an experienced senior pharmaceutical executive and was appointed CEO of the Company in July 2023. He most recently held the positions of COO, Executive Vice President, and Managing Director of Europe and International at Jazz Pharmaceuticals, following the acquisition of GW Pharmaceuticals where he served as COO, EVP, and a Board Director. Prior to GW, Chris held multiple senior commercial roles at UCB Pharma and GlaxoSmithKline in a wide range of therapeutic areas.

Dr Debra Barker - Interim Chief Executive Officer

Dr Barker has previously held positions at Novartis, Roche, GSK and most recently at Polyphor as Chief Medical and Development Officer. At Novartis, Dr Barker held several senior roles, including Head of Development for Anti-Infectives, Immunology and Transplantation. She is currently on the board of Hutman Diagnostics and BerGenBio.

Dr William Love - Founder and Chief Scientific Officer

Dr Love founded Destiny Pharma in 1997 as the co-inventor of the XF drug platform and is the named inventor of 80+ patents. He previously held senior scientist positions at Ciba Giegy / Novartis and has extensive experience in drug R&D from discovery to clinical development in the UK, EU and US. Dr Love is an expert advisory board member of Global AMR Innovation Fund, an expert panellist appointed of the UKRI Covid-19 preparedness Task Force for Research and Innovation funding and a member of the UKRI UK-China One Health Epidemic Preparedness expert panel.

Shaun Claydon - Chief Financial Officer and Company Secretary

Mr Claydon is an accomplished corporate financier and qualified Chartered Accountant with over 16 years of Board-level experience, including within the biotechnology sector. He previously served as CFO of Creabilis, CFO and chief operating officer of Orteq Sports Medicine

and has held a number of senior financial consultancy and corporate finance roles including at PwC, Evolution Beeson Gregory (Investec) and HSBC Investment Banking.

Dr Yuri Martina - Chief Medical Officer

Dr Martina has more than 20 years of experience in clinical development and has worked with key regulatory, industry and government stakeholders including the EMA, the FDA and the PMDA in Japan. He has experience in the US, Middle East and Asia and has contributed to over ten new drug product submissions to the EMA and/or the FDA. Previously Dr Martina has held positions including SVP Development and deputy CMO at Grünenthal Group and Vice President Development and Clinical Operations in Shionogi Europe. Dr Martina is a Medical Doctor and holds a PhD in Genetics and Molecular Biology, an MBA and a Master's in Project Management.

Sir Nigel Rudd - Chairman

Sir Nigel returned as Chairman of Destiny Pharma in July 2023, having previously served as Chairman of the Company between 2010 and 2018. He has held various senior management and board positions in a career spanning more than 40 years. Sir Nigel Rudd founded Williams plc in 1982, one of the largest industrial holding companies in the UK and has served in leadership roles for Alliance Boots, Signature, Heathrow, Pilkington, Meggitt and Barclays Bank.

Financial Statements

P&L

Table 21: Destiny Pharma P&L

£ 000s	2022A	2023	2024	2025	2026	2027	2028	CAGR 23-28
Revenues	**0**	**0**	**0**	**0**	**0**	**0**	**0**	
growth								
Other revenues	154	170	187	206	226	249	274	
Royalties	0	0	0	0	0	0	973	
Cost of goods	0	0	-250	-250	-250	-100	-582	
growth								
as % of sales							-5.0%	
Gross profit	**154**	**170**	**-63**	**-44**	**-24**	**-333**	**1,247**	
Gross margin	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	
S&M	0	0	0	0	0	0	0	
growth								
as % of sales								
G&A	-4,125	-4,331	-4,548	-4,775	-5,014	-5,264	-5,528	5.0%
growth	13.5%	5.0%	5.0%	5.0%	5.0%	5.0%	5.0%	
as % of sales	N/A							
R&D	-3,272	-3,599	-3,959	-4,355	-4,791	-5,270	-5,797	10.0%
growth	37.3%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	
as % of sales	N/A							
Share based payment expense	-534	-614	-706	-812	-934	-1,074	-1,235	
growth	32%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	
as % of sales	N/A							
EBIT	**-7,776**	**-8,374**	**-9,276**	**-9,987**	**-10,762**	**-11,941**	**-11,313**	
EBIT margin	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
growth	23.7%	7.7%	10.8%	7.7%	7.8%	11.0%	-5.3%	
Interest expense		0	-150	-510	-960	-1,500	-2,100	
Interest received	65	111	152	102	70	53	53	
Pre-tax profit	-7,712	-8,263	-9,274	-10,394	-11,652	-13,389	-13,360	
Tax	1,208	1,653	1,855	2,079	2,330	2,678	2,672	
Effective tax rate	-15.7%	-20.0%	-20.0%	-20.0%	-20.0%	-20.0%	-20.0%	
Net income	**-6,504**	**-6,611**	**-7,419**	**-8,315**	**-9,322**	**-10,711**	**-10,688**	
Number of shares (000s, basic)	70,182	90,100	96,046	96,858	97,792	98,865	100,100	
EPS	**-0.09**	**-0.07**	**-0.08**	**-0.09**	**-0.10**	**-0.11**	**-0.11**	
growth	**3.9%**	**-20.8%**	**5.3%**	**11.1%**	**11.0%**	**13.7%**	**-1.4%**	

Source: Intron Health estimates

Balance Sheet

Table 22: Destiny Pharma balance sheet

£ 000s	2022A	2023	2024	2025	2026	2027	2028
ASSETS							
Intangible assets	2,261	2,261	2,261	2,261	2,261	2,261	2,261
PP&E	25	26	27	29	30	31	33
Non-current assets	**2,286**	**2,287**	**2,289**	**2,290**	**2,291**	**2,293**	**2,294**
Inventories	0	0	0	0	0	0	0
Trade receivables	1,410	1,551	1,707	1,877	2,065	2,272	2,499
Other current assets	196	196	196	196	196	196	196
Cash & cash equivalents	4,903	6,191	4,361	3,663	2,987	2,953	2,974
Current assets	**6,510**	**7,939**	**6,264**	**5,736**	**5,248**	**5,421**	**5,669**
Total assets	**8,796**	**10,226**	**8,552**	**8,026**	**7,539**	**7,713**	**7,963**
LIABILITIES							
Borrowings	0	0	5,000	12,000	20,000	30,000	40,000
Other financial liabilities	0	0	0	0	0	0	0
Other non-current liabilities	0	0	0	0	0	0	0
Non-current liabilities	**0**	**0**	**5,000**	**12,000**	**20,000**	**30,000**	**40,000**
Borrowings	0	0	0	0	0	0	0
Trade payables	1,170	1,287	1,415	1,557	1,713	1,884	2,072
Provisions	0	0	0	0	0	0	0
Other current liabilities	0	0	0	0	0	0	0
Current liabilities	**1,170**	**1,287**	**1,415**	**1,557**	**1,713**	**1,884**	**2,072**
Total liabilities	**1,170**	**1,287**	**6,415**	**13,557**	**21,713**	**31,884**	**42,072**
EQUITY							
Share capital	733	733	733	733	733	733	733
Share premium	33,044	40,380	40,380	40,380	40,380	40,380	40,380
Retained earnings (losses)	-26,151	-32,174	-38,977	-46,645	-55,287	-65,284	-75,223
Total equity	**7,626**	**8,939**	**2,137**	**-5,531**	**-14,173**	**-24,170**	**-34,109**
Total liabilities and equity	**8,796**	**10,226**	**8,552**	**8,026**	**7,539**	**7,713**	**7,963**

Source: Intron Health estimates

Cash Flow

Table 23: Destiny Pharma cash flow statement

£ 000s	2022A	2023	2024	2025	2026	2027	2028
Net income	**-6,504**	**-6,611**	**-7,419**	**-8,315**	**-9,322**	**-10,711**	**-10,688**
Adjustments - finance income	-65	-111	-2	408	890	1,447	2,047
D&A	12	7	8	8	9	9	9
Share-based payment expense	534	587	617	647	680	714	749
Change in trade receivables	14	-141	-155	-171	-188	-207	-227
Change in trade payables	396	117	129	142	156	171	188
Interest paid	0	0	-150	-510	-960	-1,500	-2,100
Other movements	-281	0	0	0	0	0	0
Cash flow from operations	**-5,892**	**-6,151**	**-6,973**	**-7,791**	**-8,735**	**-10,076**	**-10,021**
Purchase of PP&E	-1	-9	-9	-10	-10	-10	-11
Interest received	65	111	152	102	70	53	53
Cash flow from investment	**64**	**102**	**143**	**93**	**60**	**42**	**42**
Proceeds from share issuance	6,086	7,337	0	0	0	0	0
Non-current debt proceeds	0	0	5,000	7,000	8,000	10,000	10,000
Cash flow from financing	**6,086**	**7,337**	**5,000**	**7,000**	**8,000**	**10,000**	**10,000**
Beginning cash & cash equivalents	**4,646**	**4,903**	**6,191**	**4,361**	**3,663**	**2,987**	**2,953**
Change in cash	258	1,288	-1,830	-698	-676	-34	21
FX impact		0	0	0	0	0	0
Ending cash & cash equivalents	**4,903**	**6,191**	**4,361**	**3,663**	**2,987**	**2,953**	**2,974**

Source: Intron Health estimates

General Disclosures and Disclaimer

Full 12-month historical recommendation changes are available on request

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