EDISON

Destiny Pharma

Eyes on the Phase IIb prize

Outlook for the clinical trial

Pharma & biotech

With the US Phase IIb study results now expected around mid-2020, we have examined the study design and our expectations for the results. Separately, we have looked beyond the current study and indication to the application of Destiny Pharma's products in infections associated with biofilms. Our valuation is £70.2m, or 160p per share.

Year end	Revenue (£m)	PBT* (£m)	EPS* (p)	DPS (p)	P/E (x)	Yield (%)
12/17	0.00	(3.21)	(8.45)	0.00	N/A	N/A
12/18	0.00	(6.01)	(11.86)	0.00	N/A	N/A
12/19e	0.25	(5.65)	(11.05)	0.00	N/A	N/A
12/20e	0.00	(6.66)	(12.91)	0.00	N/A	N/A

Note: *PBT and EPS are as reported.

Impending driver first

With all attention on the year-end interim update of the US Phase IIb study in post-operative *Staphylococcal* infections, we examine the key attributes of this study including inclusion criteria and study design, as well as the significance of and expectations for the study's endpoints. The microbiological and clinical endpoints should present few issues for an active antimicrobial such as XF-73, then attention will turn to the health economic outcomes in the Phase III studies, which are likely to determine the pricing of XF-73 gel.

Beyond the prevention of post-surgical infections

In this note we explore some of the other commercially interesting indications for the XF-series of agents. Although bacterial infections due to MRSA are associated with biofilms on catheter tips and infusion lines, for example, we focus on the higher-value biofilm-associated infections that include ventilator-associated pneumonia, cystic fibrosis and bronchiectasis.

H119 financials: Prudent management

The preparations for the US Phase IIb and the effects of the extended three-month timeline extension figured in Destiny's H119 results. We estimate FY19 total operating expenses at £7.0m (vs £6.1m in FY18) as some of the expenses of the clinical study are deferred. The H119 operating loss was driven by R&D costs of £1.7m and £0.9m in SG&A (vs £1.3m and £0.8m in H118, respectively). H119 cash was £9.1m (vs £12.1m at end FY18 and £15.1m at the end of H118). We estimate this gives Destiny a runway into 2021, by which time the Phase IIb will have reported and we expect XF-73 to have been partnered in a transaction accompanied by at least a $10m upfront payment.

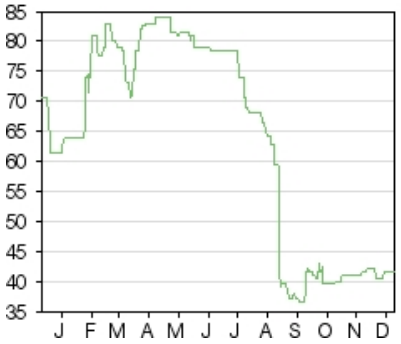
Valuation: Remains below our sensitivity analysis

We value Destiny at £70.2m, or 160p per share, reduced from £83.2m or 191p per share. This is driven by reduced pricing assumptions ($400 per XF-83 course in the US from $450), and a delay in our expected US launch (2023 from 2022), based on company guidance. However, this is still well above current market valuations, which imply pricing and probabilities of success well below historical standards.

10 December 2019

Price	**41.5p**
Market cap	**£18m**
	$1.29/£
Net cash (£m) at 30 June 2019	9.1
Shares in issue	43.9m
Free float	68.5%
Code	DEST
Primary exchange	AIM
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	0.0	7.8	(41.1)
Rel (local)	0.9	6.6	(45.7)
52-week high/low		84.0p	36.5p

Business description

Destiny Pharma is dedicated to the discovery, development and commercialisation of new antimicrobial agents that have unique properties that improve outcomes for patients. Destiny's first product, XF-73, is in a US Phase IIb clinical study.

Next events

US Phase IIb XF-73 study update	Q120
US Phase IIb study results	Mid-2020

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Edison profile page

Investment summary

A novel antimicrobial rises to meet an increasing medical need

Destiny Pharma is an antimicrobial discovery and development company whose new antimicrobial agents have unique properties that should result in improved patient outcomes. The XF series of antimicrobials are structurally and functionally distinct from all previously approved antimicrobials. Transferable resistance to the XF-series has not been detected in recent clinical isolates and de novo resistance is unlikely to occur. Destiny's antimicrobial agents have been shown to have rapid-acting bactericidal[1] activity against the most resistant bacteria, as well as antimicrobial activity across a broad range of sensitive and resistant Gram-positive and some Gram-negative pathogens. Destiny's lead product, XF-73, is in clinical development for the prevention of post-surgical infections in high-risk surgical patients. XF-73 has completed Phase I clinical studies and in 2019 commenced a US Phase IIb study that is expected to report in mid-2020. Subsequent indications for the XF-series include terminal infections, the prevention of ventilator-associated pneumonia (VAP) and biofilm-mediated infections like cystic fibrosis.

Valuation: Modest assumptions suggest material upside

Our model for Destiny Pharma uses a risk-adjusted NPV analysis resulting in a valuation of £70.2m, or 160p per share, based only on the use of XF-73 in the prevention of *Staphylococcal* post-surgical infections in high-risk surgical patients. We assume that the first XF-73 launch will be in the US, where clinical trials are now being conducted, followed by other markets including Europe (we have only included EU5), Japan (which has a history of extensive antibiotic use) and China (where Destiny already has a development and commercial agreement with China Medical System Holdings). In addition, we have assumed that, following the completion of the Phase IIb results at by mid-2020, Destiny will license XF-73 on a global basis ex-China. Our peak end-market sales forecasts for XF-73 are $1.89bn in 2028 and our valuation is based only on the royalties and milestones from the sales of XF-73.

Financials: Well funded with a validating collaboration

Destiny raised £15.2m gross in its September 2017 listing on London's AIM followed by a £3m investment by China Medical System Holdings (CMS) in December 2017 as part of a regional development and commercialisation agreement. The H119 balance sheet showed cash and equivalents of £9.1m (including term deposits of £4m). The principal H119 outlays were administrative expenses of £0.9m and R&D costs of £1.7m, which we expect to increase as the US clinical programme progresses to completion. This will be softened in FY19 by a £0.8m repayment relating to the R&D tax credit, which we also expect to move in line with R&D spend. We see Destiny funded into 2021.

Sensitivities: Right place, right time, recognition awaited

Destiny is sidestepping the problematic issues associated with the short-course treatment of infections by developing XF-73 in a preventative indication with no on-label US competition. The key sensitivities remain XF-73's price per course, market share (even though there is no approved competition) and the outcome evidence required by the FDA and payers from Phase III. Once approved, and assuming the demonstration of cost-effectiveness in high-risk patients, we believe the reimbursement of XF-73 should be easier to achieve than for acute antibiotic treatments.

[1] Bacteriostatic agents prevent bacteria from growing so that the host's immune system attacks the pathogen whereas bactericidal agents alone kill the bacteria, often resulting in lysis.

Company description

UK-based Destiny Pharma is a largely virtual (with experienced project managers who outsource much of its R&D), clinical-stage antimicrobial development company. Destiny's products are new synthetic molecular entities that have not been encountered by bacteria in nature before and are therefore not expected to be associated with bacterial resistance. Destiny's lead product XF-73 is rapidly bactericidal, offering a short-course prophylactic duration that reduces the bacterial nasal carriage burden in order to prevent infections after surgery. The FDA has agreed that XF-73 will be studied in this new preventative indication, which alone addresses most of the contemporary antimicrobial commercialisation issues. The prevention of *Staphylococcal* post-surgical infections is, like Destiny's products, novel, and no other agent has been approved for this indication in the US.

Investment proposition

Destiny Pharma is developing a novel series of antimicrobial agents that are structurally and functionally distinct from any other antimicrobial agent commercialised to date.

- Destiny Pharma is a small, UK-based anti-infective company. Its products are being developed for the US, as the launch market. Destiny's products have been licensed in a development and commercial collaboration with CMS for China.
- Destiny's antimicrobial agents are active against sensitive and resistant Gram-positive bacteria. This enables empiric prescribing (without prior susceptibility testing) because pre-existing resistance to XF-73 has not been detected and is not expected to develop. Extensive laboratory testing has failed to 'train' resistant mutants to the XF-series, nor has continued susceptibility surveillance against recent antibiotic-resistant clinical isolates detected real-world resistance. Destiny's products are being studied in indications that do not have on-label competition and are preventative, thereby avoiding the usual business case critiques associated with acute-use antimicrobial agents.
- Destiny is well-placed to take advantage of any government or industry-sponsored grants, rebates or incentives that are currently under discussion to end the drought in new antimicrobial agent development.
- Our model suggests a cash reach into 2021 – well after the US Phase IIb results will have been released and XF-73 would have been available for partnering (ex-China).
- Destiny Pharma is targeting hospital-acquired infections in high-risk cardiovascular, orthopaedic and neuro-surgical patients where the morbidity and mortality resulting from infection is high and the consequent costs to healthcare systems are significant.

Virtual company: Small attractive footprint

Destiny's costs as a small UK virtual biotech are modest for a company in mid-stage clinical development. Destiny's pipeline and development plans for its antimicrobial agents are initially in preventative indications where there is little or no competition. This has already resulted in the investment and regional development agreement with CMS. We expect this strategy to continue with the broader licensing of XF-73 once Phase IIb data has been disclosed in mid-2020. Once XF-73 has been fully out-licensed, Destiny will focus on its earlier-stage pipeline. XF-73 is the key asset on which our valuation is based.

XF-73 is a dicationic porphyrin that has rapid bactericidal activity against antibiotic sensitive and resistant Gram-positive pathogens including MRSA. These properties make the XF series ideal for an indication such as the prevention of *Staphylococcal* post-surgical infections, where the current challenges of antibiotic commercialisation (short-course acute treatments with generic substitution, resistance issues and on-label alternatives) are largely irrelevant.

The antimicrobial activity of Destiny's XF series of drugs is due to their cell surface activity, which affects at least the bacterial membrane and probably the peptidoglycan layer. Cell wall integrity is compromised by the action of the XF series, which interact with the bacterial membrane making it leaky, leading to the loss of vital bacterial intracellular components and the death of the bacteria. To prevent *Staphylococcal* post-surgical infections, XF-73 is applied topically to each nostril to reduce the asymptomatic carriage of *Staphylococcus aureus* (*S. aureus*) to a level below which the surgical wound of a high-risk patient would be likely to become auto-infected. Since the ring structure is available as a pharmaceutical intermediate, the cost of goods for XF-73 is low. No other drugs are currently approved for the prevention of *Staphylococcal* post-surgical infections or the prevention of VAP.

The commercial and unmet clinical opportunity

Destiny's XF series of antimicrobials target the large unmet need of prevention (as opposed to treatment indications where most antimicrobial agents are used) of infections in hospitals. The rise of antibiotic-resistant infections globally is well-documented,[2] but there have been commercial challenges in the development of new antimicrobials. The US Centers for Disease Control and Prevention (CDC) estimate at that least 23,000 deaths and more than two million illnesses annually in the US alone are as a result of antimicrobial resistance. Destiny's focus on prevention of infection (due to resistant and sensitive strains) rather than treatment puts it at the forefront of this market. We estimate that Destiny's XF-73 will have an addressable market of about $3.5bn in the prevention of post-surgical *Staphylococcal* infections alone (assuming 100% market share, 100% penetration). In the next section, we discuss the design and conduct of the next expected material event for Destiny Pharma: the US Phase IIb study in the prevention of post-operative surgical infections.

The next big event: The Phase IIb clinical study

The next major expected catalyst for Destiny Pharma will be the results of the US Phase IIb study of XF-73 in the prevention of *S. aureus* post-operative infections. As the study is recruiting, with an interim safety, efficacy and futility analysis scheduled for Q120 and final results expected in mid-2020, we take a detailed look at the design and our expectations for the study.

The indication is new

Many of the current investment prejudices against the development of new antimicrobial agents are perfectly valid. The most recent antibiotic to be approved in mid-August 2019 was Nabriva Therapeutics' Xenleta (lefamulin) – a systemic pleuromutilin – which was announced as a first in-class antibiotic for the treatment of community acquired bacterial pneumonia (CABP). On the day of the announcement of Xenleta's approval by the FDA, Nabriva's share price finished up less than one percent. We believe this is because, for most CABP patients, there is already cheap, effective therapy like macrolides, tetracyclines, fluoroquinolones or beta-lactams, since in the community there are lower levels of resistant bacteria than in hospitals. In addition, while Xenleta was described as a first-in-class semi-synthetic pleuromutilin antibiotic, the bacteriostatic pleuromutilins have been in human use since 2007 and even earlier in animals, and pleuromutilin resistance has been reported.

The Xenleta example provides the reasons why investors, and many pharmaceutical companies, do not find the anti-infective therapeutic area an attractive target. However, the Phase IIb study of

[2] www.cdc.gov/globalhealth/infographics/antibiotic-resistance/antibiotic_resistance_global_threat.htm

XF-73 in the prevention of *Staphylococcal* surgical skin infections addresses most of these concerns because:

- The prevention of post-operative *Staphylococcal* infections is a new indication with no other approved competition (generic or branded), although mupirocin is used off-label in the US (and is indicated to be applied twice daily for five days) but is discouraged by most anti-infective consultants on the grounds of its reservation for use in MRSA outbreaks. Because of its longer dosing schedule the usage of nasal mupirocin for the prevention of post-surgical infection is associated with compliance risks, since it would need to be applied by the patient five days prior to hospital admission.
- No resistance to XF-73 has been observed in either recent clinical isolates, or in attempts at de novo generation over many generations that have been able to generate resistant mutants against other antimicrobial agents. This was not just the limited number of generations that are associated with the emergence of resistance during treatment with the rifamycins, for example, but also beyond the number of generations that can enable bacteria to be trained to have reduced susceptibility in the laboratory to the beta-lactams and are not associated with in vivo resistance development.
- XF-73 is a bactericidal agent.
- The short administration time (four doses over 24 hours) makes it likely that XF-73 will be prescribed in hospitals before and just after surgery where compliance is higher but reimbursement is likely not to be an issue since it will absorbed within the high value disease related group code (a capitated cost) for the surgery.

What does decolonisation mean?

The Phase IIa study of XF-73 showed that *Staphylococcal* decolonisation of the potential surgical patient's nose could be accomplished by a small number of doses in a short space of time. This is important since higher compliance is associated with shorter treatment durations. In the case of the unapproved (off-label) competition, where compliance is left to the unsupervised patient at home, a few days before hospital admission and the surgical procedure, compliance is likely to be comparable to the 30% associated with primary care drugs. Therefore for XF-73, compliance and efficacy are likely to be enhanced by hospital administration in the 24 hours before and after surgery, where the patients are dosed by a healthcare professional, rather than having to remember to do it themselves at home. Nasal decolonisation is unlikely to mean sterilisation or complete elimination of *Staphylococcal* nasal carriage in most patients. More likely, nasal decolonisation means a reduction in the absolute numbers of *Staphylococci* in a pre-surgical patient's nose that significantly reduces the chances of an auto-infection.

Nasal screening for *Staphylococcal* carriage prior to surgery, although recommended in some surgical guidelines, is not largely adopted, because a negative nasal swab may not detect a transient colonisation at levels below the level of detection when the sample was taken. This 'below the level of detection' may not be 'below the level that results in an autoinfection' and this is why a short course of bactericidal agent such as XF-73 may be sufficient to 'knock down' the levels of *Staphylococci* in the nose and prevent post-surgical infections.

The reduction in colonisation and the prevention of post-operative *Staphylococcal* autoinfection is the objective of treatment with XF-73 nasal gel, not sterilisation. From a healthy microbiome perspective, transient decolonisation around the period of surgery should be important and this was demonstrated by the 60 healthy volunteer Phase IIa three-arm study (1.2mg and 0.3mg of XF-73 per dose, and placebo). As well as confirming the safety for the two doses of XF-73 gel applied to the nares twice-daily for two days, the 1.2mg and 0.3mg doses demonstrated significantly different reductions in *S. aureus* colonisation compared to placebo at days 1, 2 and 3, but by day 4 (48 hours after the last dose) *S. aureus* colonisation was again detected.

Phase IIb study design

Study NCT03915470 is a multi-centre, double-blind randomised placebo-controlled study of multiple applications of 0.2% XF-73 nasal gel, to assess its antibacterial effect on nasal *Staphylococcus aureus* carriage in patients scheduled for heart surgery. Only patients who screen positive for *S. aureus* carriage will be enrolled in the study and about 200 intent-to-treat patients are expected to be randomised 1:1 to XF-73 or placebo. One immediate advantage of this study design is the pre-selection of patients who demonstrate colonisation with *S. aureus*. One of the reasons why clinical studies on new antibiotics are done on 'all comers' – patients with either resistant or sensitive infections – is to eliminate the likelihood that too few resistant infections will not result in a statistical difference between active and placebo arms. Anti-infective clinical trials are unlikely to be powered (requiring thousands of patients) to detect an effect only in infections caused by resistant pathogens. In clinical practice, these new antibiotics are rarely used in first-line empiric therapy, or in patients infected with sensitive strains because of the much lower cost of generic antibiotic combinations that are prescribed empirically to cover and usually resolve infections caused by a range of pathogens.

As it relates to the ongoing Phase IIb study, we believe that an 'all comer' high-risk surgical patient population consists of patients who may or may not be colonised, and a low colonisation rate (akin to a low disease prevalence in one season in vaccine studies), which is typically c 30%,[3] could confound the study. The precision of the study to include only culture-confirmed high-risk surgical patients removes this confounding variable from the study design. Based on the results of the Phase IIa study (in colonised healthy volunteers), we expect the Phase IIb trial to demonstrate a significantly higher reduction in *S. aureus* colonisation (in high-risk patients) than placebo. In addition, if approved, the product may also be used in high-risk surgical patients who have not been screened. The transient nature of *S. aureus* nasal colonisation discussed above means that patients may be auto-infected, but colonisation may either not be detected per se, or not be detected in time for the surgical procedure. Furthermore, screening introduces costs and time delays that can be avoided by preventative treatment without pre-screening.

In the Phase IIb trial, either the active drug or placebo gel will be administered three times to each nostril over the 24 hours before surgery, and then a single application is administered after the closure of the surgical wound. Patients may undergo chlorhexidine skin decolonisation of the proposed surgical site ahead of surgery (as was allowed in the Phase IIa study) and prophylactic systemic antibiotics (usually a single vancomycin infusion) according to the surgeon's usual practice.

Efficacy and endpoint measures

Safety and efficacy (the latter as measured by the decolonisation of *S. aureus* from patients' noses at different time points) will be measured in the Phase IIb study, as they were in the Phase IIa study. In addition, other health economic endpoints will also be measured. The primary endpoint of the Phase IIb study will be microbiological efficacy as measured from baseline, when the patient will be colonised, until just before surgery. Secondary efficacy endpoints will follow the effect of XF-73 nasal gel on the patients' nasal *S.aureus* carriage up to six days after surgery (by which time the patients' commensal *S.aureus* carriage might be expected to have returned to baseline levels.

A key secondary endpoint is likely to be the difference between active and placebo arms, in the incidence of *Staphylococcal* post-operative infections (surgical site and bloodstream infections) in the 30-day period after surgery (90 days if the patient received an implant). In addition to this closely watched health economic endpoint, the number of prescriptions for, and the number of patients receiving anti-*Staphylococcal* antibiotics will be measured.

[3] www.ncbi.nlm.nih.gov/pmc/articles/PMC6186810/

Expectations for the Phase IIb study

Our expectations for the results of Destiny's Phase IIb study are that XF-73 gel will appear safe and microbiologically effective in eliminating nasal *Staphylococcal* carriage in patients prior to their heart surgery. If this were to be repeated in Phase III, the FDA is likely to approve XF-73 as the first drug in this indication. With today's focus on cost-effectiveness, an approval based on microbiological effectiveness is likely only to be half of the story. To gain traction with payers, surgeons and hospital administrators, decolonisation with XF-73 gel would need to show a significant reduction in post-surgical infections. This is because the direct cost of a post-surgical infection in terms of additional medicines, extended hospital stays (which in the US are over $20,000 per day) and the morbidity and mortality associated with an infection after heart surgery far outweigh the direct treatment cost of XF-73 for all high-risk surgical patients (not only those with *S.aureus* culture-positive colonisation), which we have estimated in our valuation.

While it is logical that a statistically significant microbiological reduction in nasal colonisation would also result in a statistically significant reduction in the number of *Staphylococcal* post-surgical infections in the Phase IIb study, there are dynamics that could mean that the Phase IIb demonstrates a directional benefit in infection rate, but statistical significance may have to wait for the larger patient numbers of the Phase III studies. These factors include:

- The historical post-surgical infection rate at the study centres and the way patients are processed before, during and after surgery.
- While *Staphylococcal* nasal carriage occurs in about a third of individuals, *Staphylococcal* post-surgical infection is lower, and ranges from 0.3% to 2.3% of surgical procedures.[4]
- A 200-patient, two-arm study may not have the power to detect a significant difference between study arms if conducted in a hospital with good anti-infection procedures.

With the constraints of a small biotech company, powering a much larger study to have more comfort that a statistical reduction in infection rates would be demonstrated is something better left until after Phase IIb and the deeper pockets of a partner.

Implications of the recent three-month timeline extension

In its H119 financial results, Destiny noted a three-month delay to the final results of the Phase IIb study, which are now expected in the middle of 2020. There will be an interim safety, efficacy and futility analysis by the independent drug safety monitoring board in early 2020, which we expect to be disclosed. The three-month timeline extension until the final Phase IIb study report in the middle of 2020 is required because many of the initially proposed study centres were already using a non-FDA approved pre-surgical procedure nasal decolonisation protocol. This made the use of a placebo arm in Destiny's study protocol unpalatable to these hospitals' respective local ethics committees, and additional (mostly smaller) centres were subsequently enrolled. While this resulted in a lengthened timeline for the study, conducting the study in smaller hospitals that do not have an existing nasal decolonisation policy could mean that there may be a higher post-surgical infection rate in those institutions. This could result in a higher difference in efficacy between active and control arms than would be expected from a study conducted only in large teaching hospitals, for example.

[4] www.ncbi.nlm.nih.gov/pmc/articles/PMC4229085/

Additional indications: Cystic fibrosis (CF), bronchiectasis and biofilms

There are three major diseases of the lung that are associated with mucus build-up, the inability to clear the mucus and the bacterial infections associated with excessive or dysfunctional pulmonary mucus. By comparison, the other major lung diseases are more associated with airway constriction (asthma and allergies) or fibrosis (idiopathic pulmonary fibrosis).

Mucus dysfunction pulmonary diseases

- Chronic obstructive pulmonary disease (COPD)
- Cystic fibrosis (CF)
- Bronchiectasis (BE)

While COPD and asthma are the non-cancer lung diseases with the largest number of patients, COPD as a mucus-dysfunction and inflammatory lung disease is almost always caused by prolonged exposure to tobacco smoke. The two diseases of mucus dysfunction relevant to Destiny Pharma are CF and BE. The number of patients with CF and BE is much smaller than those suffering from COPD, but this orphan indication nature makes them commercially attractive to smaller biotech companies. This is because the medical need is often much higher and the patients are under the care of specialist physicians (implying smaller sales and marketing spend) and there is usually less price sensitivity for effective therapies.

Cystic fibrosis (CF)

CF is an inherited autosomal recessive disorder that causes persistent lung infections, which over time are responsible for reduced lung capacity. CF affects about 70,000 patients globally and is therefore an orphan disease. CF is caused by one of 2,000 different loss-of-function gene mutations that encode the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Defects in the expressed CFTR protein result in secretions in the lung that do not function normally as lubricants, but are abnormally thick and sticky. This in turn results in airways that are blocked and provide a protected and nutritious home for bacterial overgrowth and, in consequence, bacterial lung infections. Repeated infections result in damage to the lung and, eventually, respiratory failure. Due to early diagnosis from pre- and post-natal screening, many more CF patients are diagnosed earlier than they would have been previously. This has resulted in a higher prevalence of disease, as has the finding that earlier treatment slows the rate of lung function decline. At the recent North American Cystic Fibrosis Conference, the predicted survival age of CF patients had risen to 41 years. Nevertheless, depending on the CFTR gene mutation, deterioration is inevitable and CF patients require daily care with physiotherapy and mucolytic enzymes to help mobilise the mucus in the lungs. Where the patient's mutation is appropriate and the reimbursement available, the small molecule CTFR modulators are the first disease-modifying drugs.

The CTFR modulators Kalydeco, Orkambi and additional experimental combinations from Vertex, while able to restore some normal function depending on the patient's CTFR mutations, appear to be much less beneficial in the amount of lung function gained, or not lost relative to placebo (measured by forced expiratory volume, or FEV_1) compared to what a pulmonologist might expect from a COPD patient receiving an inhaled corticosteroid. While Vertex's drugs are the first disease-modifying drugs in CF, their very high prices have resulted in a patient and patient group backlash in the US and the UK and France on the basis of their assessed limited cost-effectiveness.

Depending on the patient's mutation, they will still need treatments that address the symptoms of CF and these include antibiotics. The sticky mucosal environment of a symptomatic CF patient's lung is typically associated with colonisation with *Pseudomonas aeruginosa*. (*Ps. aeruginosa*) is a

highly resistant Gram-negative bacteria that often colonises, rather than infects, the lungs of CF patients although the strains isolated from CF patients are frequently capsulated – producing their own protective barrier to antibiotics or biofilm. CF patients may be colonised with *Ps.aeruginosa*, but as a low-grade pathogen, polymicrobial colonisation of the mucus with more aggressive pathogens like MRSA is likely to result in higher mortality and morbidity. That being said, inhaled antibiotics like tobramycin and the colistin-derivatives have been developed for CF patients with a Gram-negative spectrum in mind.

While colonisation and occasional infection with *Ps.aeruginosa* may punctuate the life of a CF patient, a 2010 JAMA paper[5] found that the detection of MRSA in the lungs of CF patients for longer than two years was associated with lower survival. In addition, a more recent article[6] cites the rising incidence of MRSA infection in CF patients. This is not unexpected since almost all CF patients have periods of hospitalisation during which they could be colonised by MRSA.

Bronchiectasis (BE)

Bronchiectasis (also known as non-CF bronchiectasis) is much less of an inherited condition than CF, but is often acquired as a result of a previous lung infection (like pneumonia or TB), or an inflammatory condition. Like CF, lung function declines over time with BE and about half of BE cases are idiopathic BE (with no known cause). Like CF, BE involves excessive mucus build-up but it is present as a result of scarred or inflamed airways. The complicated nature of the airways means that mucus is likely to accumulate, and bacterial infections can result. Just as in CF, the pathogens frequently associated with pneumonia in BE patients are *Ps.aeruginosa* and MRSA. The American Lung Association notes that also like CF, BE patients with MRSA infections may lose lung function at a faster rate and have more bothersome respiratory symptoms.[7]

MRSA and Destiny's antimicrobial XF-series

As we noted in our initiation, Destiny's XF-series of antimicrobials is a new class of bactericidal surface-active agents that have demonstrated preclinical and clinical activity against some Gram-negative pathogens and most Gram-positive pathogens including all *S. aureus* strains including MRSA. One distinct advantage of the XF-series of agents is that they have not been used in clinical practice to date, so no pre-existing resistance has been observed. It has not been possible to generate resistant XF-series mutants in 55 passages in the presence of low-dose XF-73 where far fewer passages have generated resistant mutants to existing antibiotics that are not normally associated with the appearance of resistance during treatment. In addition to bacteria, several fungal species have been implicated in the pathogenesis of CF and the XF-series is known to have anti-fungal activity.

In November 2018 Destiny announced that it had been jointly awarded a National Biofilms Innovation Centre-funded research collaboration with the University of Southampton to investigate the use of the XF-series of agents in preventing, controlling and eradicating chronic clinical infections with underlying biofilm involvement such as those in CF.

Part of the problem with pneumonias in CF and BE patients is that both *Ps. aeruginosa* and MRSA are difficult to treat, and both can produce their own biofilms to shelter them from the effects of antibiotics. The antibiotics used most often in CF patients are directed against the infecting pathogens and are either systemically delivered, or formulated to be delivered by nebuliser. While the formulation needed to deliver the XF-series into the lung has still to be decided, the XF-series has already shown the potential to eradicate bacteria such as MRSA within a biofilm. In addition,

[5] *Journal of the American Medical Association.* 2010;303(23):2386-2392. doi:10.1001/jama.2010.791

[6] https://doi.org/10.1164/ajrccm.179.8.734a

[7] www.lung.org/lung-health-and-diseases/lung-disease-lookup/bronchiectasis/learn-about-bronchiectasis.html

the molecular structure of the XF-series of antimicrobials, if delivered by nebuliser, could have attributes that also imply activity within a pulmonary biofilm. This is because there is a significant amount of work on the ideal properties of inhaled drugs containing quaternary amines like glycopyrronium (a drug for the treatment of COPD) and the XF-series has two important characteristics that aid retention in the lung. The first is the active uptake by epithelial cells using organic cation transporter 1, which is expressed in the lung, and the second is the retention of this type of drug in the lung because of its slower passive cellular permeability. These are a potentially validating rationale for the use of the XF-series antimicrobial agents in biofilm-mediated lung diseases like CF and BE.

Valuation

We value Destiny Pharma using a risk-adjusted NPV analysis, resulting in a valuation of £70.2m, or 160p per share based solely on the use of XF-73 in the prevention of *Staphylococcal* post-surgical infections in high-risk surgical patients. This is reduced from our previous valuation of £83.2m or 191p per share due to an adjustment in our pricing assumptions (detailed below) and pushing back the US commercialization timeline to align with company guidance. We have assumed the first launch will be in the US in 2023, as this is where Destiny's clinical trials are being conducted. This is a delay from our previous reports (2022) due to the progress of the Phase IIb study, which is expected to conclude around mid-2020. Other markets will follow, including Europe (we have only included EU5), Japan (which has a history of extensive antibiotic use, and has a pricing structure for novel drugs) and China (where Destiny already has an agreement with CMS, and there is concern on antimicrobial resistance). We have assumed that within the year following the Phase IIb results, Destiny will license XF-73 on a global basis ex-China, although regional deals may occur. Our recently revised peak end-market sales estimations and the valuation of the royalties and milestones from the sales of XF-73 are shown in Exhibit 1. Details of our typical milestone assumptions are shown in Exhibit 2. Our model also includes £0.25m in grant funding in FY19 since Destiny has received four grants since its IPO as antimicrobials are perceived to be a 'hot spot' for these incentives.

Exhibit 1: Risk-adjusted NPV valuation and XF-73 peak sales

Product	Jurisdiction & launch price per course ($)	Launch	Peak sales ($m)	NPV (£m)	NPV/share (£)	Probability	Licensing deal probability	rNPV (£m)	rNPV/ share (£)
XF-73	US – 400	2023	1,490						
XF-73	Japan – 350	2024	39						
XF-73	EU5 – 220	2023	302						
XF-73	China - 100	2024	62						
XF-73 royalties				287.2	6.5	35%	70%	55.6	1.3
XF-73 milestones				79.1	1.8	35%	70%	19.8	0.5
Unallocated costs				(10.7)	(0.2)	35%	100%	(14.2)	(0.3)
Net Cash/(Debt)				9.1	0.2	100%	100%	9.1	0.2
Valuation				364.8	8.3			70.2	1.60

Source: Edison Investment Research. Note: Number of shares = 43.9m. Net cash includes term deposits.

Our assumptions on XF-73 are modest

We have confined the use of XF-73 to the indication for the prevention of post-operative *Staphylococcal* infection in only high-risk patients. The preventative indication (to which the FDA has agreed) avoids the commercial issues involved with treating only infected patients with a short course therapy. Instead, the preventative indication covers a significantly larger number of asymptomatic surgical patients prophylactically treated for a short course. We have further restricted our model only to some cardiovascular surgeries (not including interventional cardiology indications, for example), neurosurgical indications (with spinal injections and carpel tunnel release

procedures excluded) and orthopaedic surgeries (excluding bunion surgery, knee arthroscopy and muscle, tendon, facia and bursae procedures).

The reported incidence of high-risk surgical procedures differs by market, with the US having the most complete data (of 48.3m surgical procedures in 2010, 6.6m were high risk). The Chinese market has a lower recorded number of high-risk surgeries, and we have assumed a lower penetration rate and market share in China compared to other markets for the initial two-year period after launch and before access to the National Drug Reimbursement List (NDRL). After access to the NDRL, we have assumed that the price per course falls from $100 to $50, but the market share triples (as was the case with Roche's Avastin). As XF-73 is expected to complete and report the Phase IIb results in mid-2020, we have applied a 35% probability of success with a 70% chance of a licensing deal (since there is already a regional development deal with CMS). We will revisit the deal terms and probabilities after the Phase IIb results. As there is considerable scope to alter the probabilities of success for anti-infectives, we have revised our sensitivity analysis (Exhibit 3, below). The effect of these base case assumptions on end-market sales of XF-73 is shown in Exhibit 1. The other key assumptions in our model include:

- We expect US pricing of $400. This is reduced from our previous assumption of $450 on the basis of company guidance. This still, however, represents a premium to the existing off-label standard of care (Bactroban Nasal, with a list price of about $300 for a five-day course) because XF-73 will be the first drug approved in the prevention of post-surgical infections, will have a shorter course of administration than the off-label product and is not expected to be associated with the risk of treatment failures due to resistance. The impact on the valuation of the reduction in price is partially offset by increased uptake, as we expect this price point to face less reimbursement resistance.
- We have used our typical international pricing index to result in an XF-73 price per course of $350 in Japan (from $400), $220 in Europe (from $250) and $100 in China (unchanged).
- We have assumed that 90% of all high-risk surgical patients are treated prophylactically with an antibiotic in all markets except China (10%), since the morbidity and mortality costs of a post-surgical infection in cardiovascular, neurosurgical or orthopaedic patients, including the extra days of hospital stay, far outweigh the costs of prophylactically treating all high-risk surgical patients.
- We have assumed a 60% peak market share in all markets except China (where we have assumed 30% initially), even though there will be no on-label competition and XF-73 is not expected to be associated with resistance. We have assumed generic erosion on the expiry of the US patent in 2030 (2031 in the EU5), following which we forecast that XF-73 sales decline rapidly.
- For valuation purposes only, our licensing deal terms remain modest with milestones that start at $10m in 2020 and total $190m, and a 10% royalty on net sales, as detailed in Exhibit 2. We have adjusted the timeline of these milestones from previous reports to align with a US launch in 2023 (from 2022 previously).

Exhibit 2: XF-73 milestone and royalty assumptions

Milestone/royalty	Date	Rate/value ($m)
Royalty rate	From 2023	10%
Collaboration agreement	2020	10
Phase III start	2021	5
NDA filing	2023	5
Approval/launch	2023	10
$50m global sales hurdle	2024	10
$100m global sales hurdle	2025	20
$300m global sales hurdle	2026	30
$500m global sales hurdle	2026	50
$1bn global sales hurdle	2027	50
Total milestone value ($m)		**190**

Source: Edison Investment Research

Sensitivities

We have valued Destiny Pharma based solely on the sum of the milestones and royalties from a licensing deal for its lead product, XF-73. Destiny is developing other XF series products, including for the prevention of VAP, the treatment of CF and dermal indications – VAP is a smaller number of patients, but a higher value per patient – and other earlier-stage products that have in vitro activity against biofilms.

Destiny is developing first-in-class antimicrobial agents as the first drugs to be approved in those indications. Therefore, clinical, regulatory and commercial risks may apply.

Some key sensitivities apply in our XF-73 model. After antimicrobial products have shown biological activity in animal models, their subsequent development is generally less risky than oncology or neurology drugs as the resolution of an infection in mice is predictive of one in humans. For instance, in 2003 CMS reported that the probability of a Phase II anti-infective product reaching the market was 47% vs 2% for a CNS drug at the same stage of development. Even the 47% probability explored in Exhibit 3 may be an underestimation since it would apply to all antimicrobials – systemic and topical – and topical agents like XF-73 generally have far fewer toxicological issues. Exhibit 3 explores the revised sensitivity of the risk-adjusted valuation of Destiny Pharma (inclusive of net cash) to clinical trial probabilities at Phase II and the price per course of XF-73, with all other assumptions remaining unchanged.

Exhibit 3: Sensitivity analysis of rNPV per share (£) of the XF-73 price per course vs clinical trial probability of success (%)

Probability of success	US price per course ($) (other markets indexed to the US)				
	$60	$300	$400	$500	$600
20%	0.46	0.80	0.94	1.08	1.22
35%	0.77	1.36	**1.60**	1.85	2.09
47%	1.01	1.80	2.13	2.46	2.79

Source: Edison Investment Research

The price of a branded drug will almost always be a key driver of the valuation of the company. While off-label but branded Bactroban Nasal (mupirocin calcium) is priced at about $300 per five-day course, we have assumed a price per course of $400 for XF-73 because its profile is expected to have advantages over the off-label competition. XF-73 is active against strains that are mupirocin-resistant, has a shorter course than Bactroban Nasal, and most importantly, because XF-73, unlike Bactroban Nasal, is expected to be the only drug approved for the prevention of *Staphylococcal* post-surgical site infections. Another possible competitor to XF-73 is intravenous vancomycin, which costs hospitals c $60 per bag. Vancomycin is a valuable drug that retains activity against antibiotic-resistant bacteria and, while some surgeons infuse a single bag before each surgery, it is neither approved for this indication nor included in surgical guidelines. The use of

vancomycin in surgical prophylaxis is also discouraged by infectious disease physicians on the grounds that it promotes resistance. However, we have included $60 as the bottom end of the pricing range in Exhibit 3. The prices in each market are linked to the US price of $400 in our model so that when this changes in the sensitivity analysis in Exhibit 3, it feeds through to all jurisdictions.

From the analysis in Exhibit 3, it appears that at a price of c 46p per share, which is roughly similar to the company's current share price, the market is effectively assuming a price per course for XF-73 that is significantly below all other branded and unapproved competitors, and less than a 20% probability of success for the anti-infective product that already showed efficacy in Phase IIa.

Financials

Destiny raised £15.2m gross in its September 2017 listing on London's AIM, followed by a £3m investment by China Medical System Holdings (CMS) in December 2017 as part of a regional development and commercialisation agreement. This included rights to Destiny's pipeline in China and some other Asian countries (excluding Japan). The end-H119 balance sheet showed cash and equivalents of £9.1m (including £4.0m in term deposits). Even with Destiny's investment in its ongoing US Phase IIb study, the H119 total operating expense was £2.5m compared to £2.6m in H118. Part of the reason for this lower operating expense was the delay in opening centres for the Phase IIb study, grant funding of its earlier-stage pipeline and the R&D tax credit. These contributed to Destiny's H119 loss per share of 4.8p (5.2p per share in H118). We have slightly adjusted our expected operational loss for FY19 to £5.7m from £6.7m as we have offset some R&D expenses into 2020.

Destiny believes that it has enough financial resources to last into 2021, and that they should be enough to carry Destiny through to its key inflection points in 2020 (including the Phase IIb study read-out in mid-2020). Our financial model projects Destiny's expected spend on the US Phase IIb clinical study and includes a very modest, non-dilutive grant funding inflow of £0.25m in FY19. We have included placeholder funding of £7.8m ($10m) in 2020 since we now forecast that the funds raised in the 2017 IPO will allow operation through 2021, before which we expect either a $10m (assumed for the purpose of our model as illustrative debt) licensing transaction for XF-73 or a fund-raising to provide funds to further develop Destiny's pipeline beyond 2021.

Exhibit 4: Financial summary

Accounts: IFRS; year end 31 December; £000s	2017	2018	2019e	2020e
INCOME STATEMENT				
Total revenues	-	-	250	-
Cost of sales	-	-	-	-
Gross profit	-	-	250	-
SG&A (expenses)	(1,689)	(1,863)	(2,057)	(1,700)
R&D costs	(820)	(3,474)	(3,900)	(5,000)
Other income/(expense)	0	-	198	-
Exceptionals and adjustments	(710)	(738)	(219)	(25)
Depreciation and amortisation	(2.1)	(9.7)	(2.3)	(2.3)
Reported EBIT	(3,222)	(6,084)	(5,729)	(6,727)
Finance income/(expense)	10.5	76.0	80.6	65.1
Reported PBT	(3,211)	(6,008)	(5,649)	(6,662)
Income tax expense (includes exceptionals)	234	841	800	1,000
Reported net income	(2,977)	(5,167)	(4,849)	(5,662)
Basic average number of shares, m	35,254	43,563	43,734	43,865
Basic EPS (p)	(8.45)	(11.86)	(11.05)	(12.91)
BALANCE SHEET				
Property, plant and equipment	22.3	30.4	38.0	36.2
Goodwill	-	-	-	-
Intangible assets	-	-	-	-
Other non-current assets	-	-	-	-
Total non-current assets	22.3	30.4	38.0	36.2
Cash and equivalents	11,724	7,061	1,918	4,885
Other financial assets (term deposits)	5,000	5,000	4,000	4,000
Inventories	-	-	-	-
Trade and other receivables	277	931	1,259	277
Other current assets	60	36	186	186
Total current assets	17,061	13,028	7,363	9,348
Non-current loans and borrowings	-	-	-	7,752
Other non-current liabilities	-	-	-	-
Total non-current liabilities	-	-	-	7,752
Trade and other payables	152	404	283	152
Current loans and borrowings	-	-	-	-
Other current liabilities	246	398	246	246
Total current liabilities	397	802	529	397
Equity attributable to company	16,686	12,257	2,675	(2,965)
Non-controlling interest	-	-	-	-
CASHFLOW STATEMENT				
Profit for the year	(3,211)	(6,008)	(5,649)	(6,662)
Taxation expenses	-	-	-	-
Profit before tax	(3,211)	(6,008)	(5,649)	(6,662)
Net finance expenses	(10)	(76)	(81)	(65)
EBIT	(3,222)	(6,084)	(5,729)	(6,727)
Depreciation and amortisation	2.1	9.7	9.7	2.3
Share based payments	710	738	219	25
Other adjustments	-	-	-	-
Movements in working capital	165	381	(1,515)	850
Interest paid / received	-	-	-	-
Income taxes paid	192	234	800	1,000
Cash from operations (CFO)	(2,153)	(4,721)	(6,216)	(4,850)
Capex	(23.2)	(17.8)	(15.2)	(0.5)
Acquisitions & disposals net	-	-	-	-
Other investing activities	(4,990)	76	1,081	65
Cash used in investing activities (CFIA)	(5,013)	58.2	1,065.4	64.6
Net proceeds from issue of shares	17,409	-	7	-
Movements in debt	-	-	-	7,752
Dividends paid	-	-	-	-
Other financing activities	-	-	-	-
Cash from financing activities (CFF)	17,409	-	7	7,752
Currency translation differences and other	-	-	-	-
Increase/(decrease) in cash and equivalents	10,243	(4,663)	(5,143)	2,967
Currency translation differences and other	-	-	-	-
Cash and equivalents at end of period	11,724	7,061	1,918	4,885
Net (debt) cash (includes Term Deposits)	16,724	12,061	5,918	1,133
Movement in net (debt) cash over period	15,243	(4,663)	(6,143)	(4,785)

Source: Destiny Pharma accounts, Edison Investment Research

Contact details	Revenue by geography
Destiny Pharma Sussex Innovation Centre Science Park Square, Falmer, Brighton, UK, BN1 9SB +44 (0) 1273 70444 www.destinypharma.com/	N/A

Management team

CEO: Neil Clark	CSO: Dr William Love
Neil joined Destiny in 2017 and is an accountant by training. He joined CeNeS Pharmaceuticals, a venture capital-backed private UK biotech company in 1997. He was involved in the flotation of CeNeS in 1999 on the London Stock Exchange and subsequently appointed CFO. In 2001 he became COO as well as CFO, overseeing a restructuring of the business. He became CEO in 2005 and led the company through to its sale in 2008. More recently, Neil was CFO of Ergomed from 2009, through its IPO in 2014 until his move to full-time CEO of PrimeVigilance (Ergomed's successful drug safety business) in 2016.	Bill is Destiny's founder and CSO, having previously been a senior scientist at Ciba Geigy/Novartis. He was involved in developing the world's first leading eye care pharmaceutical, Visudyne. In 1997, he founded Destiny Pharma and he is the co-inventor of the XF drug platform. Bill was a founding member of the BEAM Alliance, an EU SME group focused on promoting antimicrobial drug development. He is an Expert Advisory Board member of Global AMR Innovation Fund, appointed by Professor Dame Sally Davies in October 2016. He has experience in drug R&D from discovery and lead identification, through preclinical development to Phase I/II clinical development in the UK, EU and US.
CFO: Shaun Claydon	**Chairman: Nick Rodgers**
Shaun is an experienced corporate financier and qualified chartered accountant with over 16 years' board level experience, including within the biotechnology sector. He has extensive experience of delivering financial and operating results and from 2015 served as CFO of Creabilis, a venture backed clinical-stage specialty pharmaceutical company focused on dermatology treatments, during which he led the $150m sale of the business to Sienna Biopharmaceuticals. From 2009 to 2014 Shaun was CFO and chief operating officer of Orteq Sports Medicine, a medical device company and world leader in the field of biodegradable polymer technologies. Prior to these positions he held a number of senior financial consultancy and corporate finance roles including at PwC, Evolution Beeson Gregory (now Investec) and HSBC Investment Banking.	Nick has considerable board experience in both public and private growth companies, particularly those in the life science sector, as well as a background as a successful corporate financier and investment banker. He is currently chairman of SEHTA, one of the largest health technology networking organisations in the UK. Prior to this, he was non-executive director and then chairman of fully listed Oxford Biomedica, between 2004 and 2016. Previously, Nick headed up both the Life Science and Corporate Finance departments at Evolution Beeson Gregory (now Investec) advising many listed life science companies from 1989 until 2003.

Principal shareholders	(%)
William Love	15.6
Wade family	13.6
Canaccord Genuity Group Inc	10.9
Rosetta Capital V LP	7.0
Eagle, J.	5.2
A&B HK Co Ltd	4.4
CMS Medical Venture Investment	4.4

Companies named in this report

Roche (ROG.SW), Ergomed (ERGO), Oxford Biomedica (OXB), Vertex (VRTX)

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