

# Destiny Pharma

## Destiny beguiles

Destiny Pharma is a virtual antimicrobial discovery company in Phase II clinical studies in the US. Destiny's XF series of antimicrobial agents are novel, rapidly bactericidal and not associated with bacterial resistance, which typically limits the use of other antimicrobial agents. This makes Destiny's lead product, XF-73, ideal for the prevention of post-operative infections, an indication in which no other drugs have been approved. We forecast Destiny's cash reach to at least 2020, with Phase IIb results for XF-73 available at the end of 2019.

Year end	Revenue (£m)	PBT* (£m)	EPS* (p)	DPS (p)	P/E (x)	Yield (%)
12/16	0.0	(1.45)	(3.94)	0.0	N/A	N/A
12/17	0.0	(3.21)	(8.45)	0.0	N/A	N/A
12/18e	0.0	(7.38)	(14.43)	0.0	N/A	N/A
12/19e	0.5	(8.31)	(15.40)	0.0	N/A	N/A

Note: \*PBT and EPS are on reported basis.

## Novel anti-infectives: The environment is aligning

The US Centers for Disease Control and Prevention (CDC) has estimated that antibiotic resistance causes at least 46,000 deaths per year in the EU and US. While governments and the World Health Organization (WHO) are concerned with this increasing problem, Destiny has directed its R&D towards products that are active against both sensitive and resistant bacteria. In addition, its first indication for post-surgical site infection prevention has been endorsed by the FDA and neatly sidesteps the commercial issues that other companies have encountered in the development of new antimicrobial agents for the treatment of acute infections, by using preventative indications.

## XF-73, first-in-class antimicrobial in a new indication

XF-73 (exeporfinium chloride) is Destiny's lead bactericidal antimicrobial product. Laboratory studies have not detected bacterial resistance to XF-73 in clinical isolates, and it has not been possible to generate it. One of the common criticisms of the new antibiotic therapeutic area is the difficulty in commercialising products that are only administered for short periods of time. Destiny avoids this issue with XF-73, which is indicated for the prevention of post-surgical infections. XF-73 has no on-label competition in the US in this new indication and its lack of resistance and bactericidal activity suggest an ideal profile for the empiric prevention of infections.

## Valuation destined to reflect value generation

We have analysed Destiny Pharma using a risk-adjusted NPV model resulting in a valuation of £89.1m or £2.04 per share, based only on the use of XF-73 in the prevention of *Staphylococcal* post-surgical infections in high-risk surgical patients. We have assumed the first launch will be in the US in 2022, although it has already partnered in China, and the results of the Phase IIb clinical study, which was fully funded by the IPO proceeds, could enable Destiny to enter into a global licensing transaction on XF-73 as soon as 2020.

Initiation of coverage

Pharma & biotech

4 September 2018

**Price** **87.5p**

**Market cap** **£38m**

\$/£1.28

Net cash (£m) at 31 December 2017 16.7

Shares in issue 43.56m

Free float 92.7%

Code DEST

Primary exchange AIM

Secondary exchange NA

### Share price performance



% 1m 3m 12m

Abs (13.4) (21.5) (44.3)

Rel (local) (12.0) (19.7) (45.1)

52-week high/low 235.0p 87.5p

### Business description

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

### Next events

Interim results 26 September 2018

US Phase IIb start XF-73 Q119

Final US Phase IIb XF-73 study data Q419

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**Destiny Pharma is a research client of Edison Investment Research Limited**

## Investment summary

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### Novel antimicrobial meets unmet need

Destiny Pharma is an antimicrobial discovery, development and commercialisation company. Its 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 previous antimicrobials. Transferable resistance to Destiny's drugs has not been detected in clinical isolates and *in vitro* passage data have suggested that resistance is unlikely to occur. Destiny's antimicrobial agents have been shown to have fast-acting bactericidal activity against the most resistant bacteria – methicillin-resistant *Staphylococcus aureus* (MRSA) – and have demonstrated antimicrobial activity across a broad range of sensitive and resistant Gram-positive and some Gram-negative pathogenic bacteria. Destiny's lead product, XF-73, is in clinical development for the prevention of post-surgical infection in high-risk surgical patients. XF-73 has completed European preclinical and clinical studies and in February 2018 received IND clearance to commence US clinical studies, the first of which – a skin irritation study – completed in July. The subsequent indications of the prevention of ventilator-associated pneumonia (VAP) and skin infections are also being investigated, currently preclinical and with a different formulation. Earlier-stage opportunities include the potential for Destiny's antimicrobial agents to treat conditions where biofilms are involved and a recent collaboration with Aston University has been announced.

### Valuation: Modest assumptions suggest material upside

We model Destiny Pharma using a risk-adjusted NPV analysis resulting in a valuation of £89.1m or £2.04 per share, based only on the use of XF-73 in the prevention of *Staphylococcal* post-surgical infections in high-risk surgical patients. We have assumed the first 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 agreement with China Medical System Holdings). We have assumed that, following the completion of the Phase IIb results at the end of 2019, Destiny will license XF-73 on a global basis ex-China. Our peak end-market sales forecasts for XF-73 are \$1.87bn in 2029 and our valuation is based only on the royalties and milestones from the sales of XF-73.

### Financials: Well-funded with a collaboration to boot

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 end-2017 balance sheet showed cash and equivalents of £16.7m (including term deposits of £5m). The principal 2017 outlays were admin expenses of £2.5m (including £0.5m listing costs) and R&D costs of £0.8m, which we expect to increase as the US clinical programme progresses. This was softened by a £0.2m repayment relating to the R&D tax credit, which we also expect to increase in line with R&D spend. We see Destiny funded at least until the end of 2020.

### Sensitivities: Right place, right time

Destiny has neatly sidestepped 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, the reimbursement of XF-73 should be easier to achieve than for acute antibiotic treatments.

## Company description

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UK-based Destiny Pharma uses a virtual model (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 associated with the bacterial resistance. Destiny's lead product XF-73 is rapidly bactericidal, offering short-course durations that reduce the bacterial nasal carriage burden and prevent infections after surgery. The FDA has agreed that XF-73 will be studied in a preventative indication and this addresses most of the contemporary antimicrobial commercialisation issues. The prevention of *Staphylococcal* post-surgical infections is, like Destiny's products, a new indication, for which no other agent has regulatory approval.

## Investment proposition

Destiny Pharma is developing a completely new 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 whose products are being developed for the US market in the first case and have already been licensed for China in a regional development collaboration with CMS.
- Destiny's products are active against sensitive and resistant Gram-positive bacteria enabling empiric prescribing because pre-existing resistance to XF-73 has neither been detected nor is it likely to develop. 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 antimicrobials.
- 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. The antimicrobial drug development space has been a hotspot for big pharma M&A since most companies have withdrawn from R&D in this therapeutic area, but big pharma companies have continued to acquire companies like Cubist for their public profile value and commercial hospital product infrastructure.
- Our model suggests a cash reach until at least 2020, a year after the US Phase IIb results will have been presented and XF-73 will have been available for partnering (ex-China).

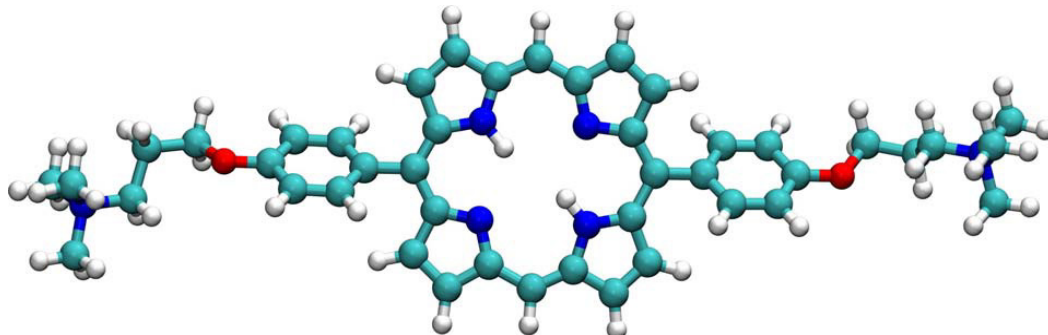
Destiny Pharma is targeting hospital-acquired infections in high-risk cardiovascular, orthopaedic and neuro-surgical patients where the morbidity and mortality resulting from infection is high and the consequent costs to healthcare systems are significant.

## Virtual company – small attractive footprint

Destiny's costs as a small UK virtual biotech are modest for a company in clinical development. Destiny's pipeline and development plans for its antimicrobial agents are in preventative indications with 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 have been disclosed towards the end of 2019. Once XF-73 has been fully out-licensed, Destiny will focus on its earlier-stage pipeline products. XF-73 is the key asset on which our valuation is based.

XF-73 is a dicationic porphyrin that is rapidly bactericidal against sensitive and resistant Gram-positive pathogens including MRSA. These properties make the XF series ideal for an indication such as the prevention of 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.

**Exhibit 1: Molecular structure of XF-73 exeporfinium chloride**



Source: Destiny Pharma

The antimicrobial activity of Destiny's XF series of drugs is due to their cell surface activity, which affects at least the bacterial membrane (see Exhibit 2) and probably the peptidoglycan layer. Cell wall integrity is compromised by the action of the XF series, which interacts with the bacterial membrane making it leaky, leading to the loss of vital bacterial intracellular components and the death of the bacteria. To prevent 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 be 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. We discuss XF-73 and its context in more detail from page 5 onwards.

## The commercial and unmet clinical opportunity

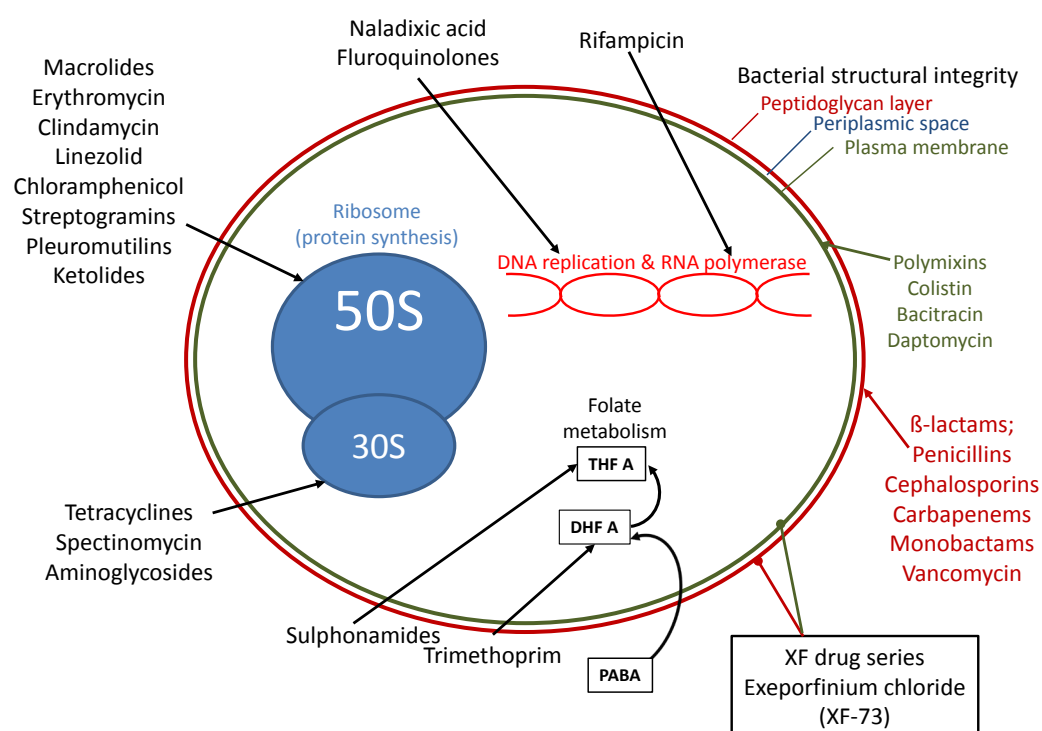
Destiny's XF series of antimicrobials target the large unmet need of prevention (as opposed to treatment) of infections in hospitals. The rise of antibiotic-resistant infections globally is well-documented,<sup>1</sup> but there have been commercial challenges in the development of new antimicrobials. The US Centers for Disease Control and Prevention (CDC) estimates that at 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 (100% market share, 100% penetration). In the next section, we discuss the history of antimicrobials in the light of the challenges that have arisen and describe how Destiny's strategy of new preventative indications and the activity of the XF series against sensitive and resistant bacteria addresses those issues.

<sup>1</sup> [https://www.cdc.gov/globalhealth/infographics/antibiotic-resistance/antibiotic\\_resistance\\_global\\_threat.htm](https://www.cdc.gov/globalhealth/infographics/antibiotic-resistance/antibiotic_resistance_global_threat.htm)

## The challenges of antimicrobial commercialisation and bacterial resistance

Antimicrobial agents (antimicrobials) are a broad group of active pharmaceutical ingredients that either kill microorganisms (bactericidal agents) or stop their growth (bacteriostatic agents). The static or cidal activity is largely independent of the site of action, although on the whole agents that target the bacterial ribosome are frequently static, while the inhibition of cell wall synthesis (by the  $\beta$ -lactams, for example) is mainly bactericidal. A summary of the site of action of the common classes of antimicrobial agents, and Destiny Pharma's lead product XF-73 in Gram-positive bacteria, is shown in Exhibit 2. XF-73 is rapidly bactericidal and has a unique cell surface-active mode of action which, in part, explains the lack of resistance observed to date. Antimicrobial agents are generally cheaper to produce from widely available chemical intermediates than antibiotics, which need a large fermentation campaign infrastructure.

**Exhibit 2: Mechanism of action of common antimicrobial agents and XF-73**



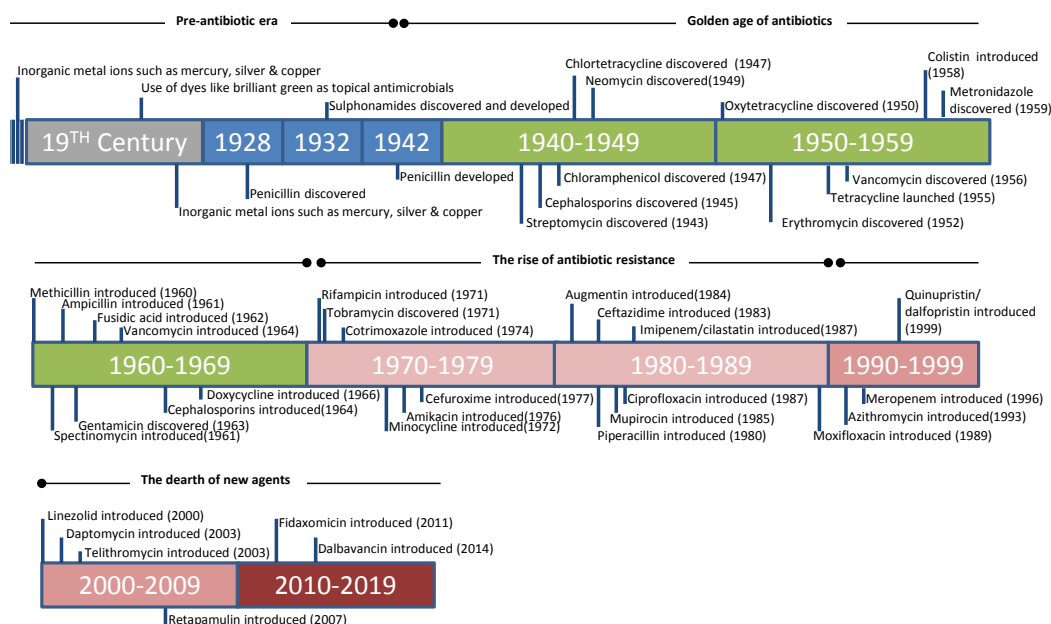
Source: Edison Investment Research

The original non-antibiotic antimicrobial agents were inorganic elements like silver, arsenic and mercury. These had been used since before the 19th century but were limited by their systemic toxicity in humans. This initial non-antibiotic era was capped by the discovery of the sulphonamide class of drugs that were widely commercialised soon after discovery but now bacteria sensitive to the sulphonamides are very rare. The golden age of antibiotics started in 1942 after the academic discovery of penicillin in 1928 was accelerated as a result of the need to treat infections as part of the war effort. Penicillin became the first commercially available antibiotic (rather than antimicrobial agent).

The history of antimicrobial discovery (Exhibit 3) underplays the number of individual antibiotics approved in the period to the late 1980s, with many members of each class becoming available. Destiny Pharma's XF series of antimicrobial agents is a completely new set of molecular entities that differ from any listed in Exhibit 3. When new antimicrobial agents were approved before the late 1980s, they were generally indication-independent and the physician decided which antibiotic

was most appropriate for the infection. Since the late 1980s, approvals have been indication-specific and this relates to some of the commercial issues discussed below. Destiny Pharma has addressed these issues with its first two products by choosing (with the FDA's endorsement) new preventative indications.

### Exhibit 3: An abbreviated history of antimicrobial agent development



Source: Edison Investment Research

Preventative indications, although of short treatment duration, are administered (like preventative vaccines) to many more patients at risk of a surgical site infection than only those who develop an infection and require treatment. The first phase of the antibiotic era lasted until the 1980s and saw the introduction of many classes of new antibiotics. Vancomycin for example, remains in use today but is reserved for the treatment of resistant infections. The distinction between naturally produced antibiotics and non-antibiotic synthetic antimicrobials became blurred in this later period, with antibiotics like chloramphenicol – which had a small molecular weight – able to be fully (and more cheaply) synthesized without fermentation. Destiny Pharma's products are synthetic antimicrobial agents. In addition, the further application of medicinal chemistry to the field resulted in chemically modified antibiotic structures that had either increased antibacterial activity or spectrum, or enabled oral administration.

Towards the end of the 1980s, three factors came into play that together resulted in the number of available active antibiotics declining. The old pharmaceutical model of developing a new antimicrobial for the retail market, so that millions of prescriptions could be written by thousands of primary care physicians who were visited by thousands of sales reps every day, fell out of favour as some of those original blockbuster drugs went off-patent and the return on that investment was not justified. This resulted in a revised focus on hospital and specialist drugs. There was also an industry-wide feeling that with so many antimicrobial agents available, there was little commercial need to develop new ones.

## The rise of antimicrobial resistance

Apart from the structural class, the classification of antimicrobial agents can also be based on their spectrum of activity. This is typically a binary classification into broad- and narrow-spectrum agents, although many experts also use the terms broad- and narrow-spectrum activity within the two main groupings of bacteria, Gram positives and Gram negatives. Broad-spectrum antibiotics that have



retained activity across Gram-positive and Gram-negative organisms are uncommon today. Destiny's XF series of agents have an antimicrobial spectrum that includes Gram-positive and some Gram-negative bacteria.

The widespread use of antibiotics in humans and animal husbandry resulted in the predomination of bacterial resistance. In the early days after the discovery of penicillin, pathogens such as *S.aureus* were almost universally sensitive to the drug. Since the 1980s, penicillin-sensitive *S.aureus* clinical isolates became rare and are almost unknown today. Bacterial resistance is thought to have originally evolved in the soil in bacteria that were in proximity to antibiotic producing fungi in order for the bacteria to survive. Destiny's products, and the XF series specifically, are not antibiotics and are made synthetically from intermediates. Widespread bacterial resistance to antibiotics was probably inevitable and would eventually limit the commercial lives of products even before patent expiry. Destiny's products have not existed in nature and can therefore be expected to have clinical utility without resistance for a significantly longer time than traditional antibiotics.

Today, bacterial resistance to antibiotics is widespread and a considerable concern, especially in hospitals where the selection pressure is highest and the patients who may be infected are most fragile. The WHO recently cited antibiotic resistance as one of the largest global threats to health and development. This presents governments with a significant problem, as they face scenarios not dissimilar to the days before antibiotics were available when common infections could not be treated and became life-threatening. Combinations of antimicrobial agents, rather than novel agents, were the main source of new antimicrobials in the post-golden age period from the 1990s onwards, and completely new active antimicrobial agents like Destiny Pharma's products remain rare discoveries.

## The commercialisation challenges of antimicrobial therapies

By the early 1980s, the pharmaceutical sector saw its job in developing new antimicrobial agents as largely done. This was because multiple members from many classes were available, and generic competition and indication-specific approvals discouraged the development of new agents. At that time, the approval of antimicrobial agents for a specific indication may not have been thought of as a hindrance to commercialisation. However, today the off-label prescribing of antimicrobial agents outside their approved indications presents a number of commercial barriers:

- Reimbursement becomes more difficult unless the prescription is for the approved indication (slightly less of an issue in hospitals).
- For indications where the outcome can be serious, or at least where resolution can be delayed by bacterial resistance, litigation risks may apply for agents not FDA approved for that particular indication (in the US).
- Indication-specific prescribing tends towards following guidelines that often have cheaper, generic drugs as the first-line option.

Thus, when the second-generation  $\beta$ -lactams like cefuroxime started to go off-patent, there was less of an incentive to develop new antibiotics that would either compete with cheaper generic versions or be reserved to later lines of therapy in smaller numbers of patients. At that time, particularly in Japan where antibiotic overuse was common, resistance to antibiotics started to be a problem. The development and commercialisation of hospital antibiotics continued because hospital antibiotics require less marketing effort than is required in primary care, and hospital infectious disease (ID) specialists were an easier group of physicians to target and reach. Pharmaceutical development strategy is something of a super tanker; once it changes direction, it is difficult to change again. As the number of newly launched antibiotics fell and resistance to those already available rose, the big pharmaceutical companies had already largely disbanded their discovery and development efforts, leaving those that were developed and commercialised to the smaller biotech companies.

Another reason big pharmaceutical companies left the antimicrobial agent space was because they could see more valuable opportunities in other therapeutic areas. Antimicrobial drugs are usually only dosed for five to 12 days until the infection is resolved and the patient is cured. In areas like oncology and neurology, patients need chronic dosing, often for the rest of their lives. Outside of the lifetime dosing associated with HAART for HIV infection and perhaps antibiotic prophylaxis in cystic fibrosis patients, other non-antimicrobial and chronically dosed indications became more commercially attractive to big pharma companies than antimicrobial agents.

## **Non-dilutive incentives are common**

Today, the sector is experiencing severe challenges on new antimicrobial agents. Almost no new antibiotic classes have come to the market for about a decade and, at the same time, transferable resistance to the existing classes has reduced the number of therapeutic options. To combat this 'antibiotic crisis', a number of initiatives have been proposed to encourage antimicrobial drug development:

- FDA and EMA fast-track designations that enable faster submissions and regulatory reviews.
- FDA Qualified Infectious Disease Product Designation (QIDP) granted under the Generating Antibiotic Incentives Now (GAIN) legislation, with priority review on first application and five years of additional market exclusivity. This has already been awarded to Destiny.
- The US 21st Century Cures Act, which may allow the FDA to accept surrogate (microbiological) endpoints, rather than a clinical (number of post-surgical infections) endpoint. The former is faster to measure.
- The REVAMP Act 2018 is US bipartisan legislation to incentivise antimicrobial development including an extra year of market exclusivity (peak sales).
- New technology add-on payments (NTAP) have recently been granted by CMS to encourage the use of antibiotics in new hospital indications, providing additional funding for products that would not otherwise be covered by Medicare on their introduction.

## **Destiny does it differently – prevention rather than cure**

Destiny has clearly learnt from the period from 2000 onwards when smaller biotechnology companies became the main developers of new antimicrobial agents. One example is Cubist Pharmaceuticals, which developed Cubicin (daptomycin), a new member of the injectable lipopeptide class of antibiotics, approved by the FDA in 2003 only for skin infections. Daptomycin was originally developed by Eli Lilly, although it was dropped on safety grounds and out-licensed to Cubist. Once approved Cubicin's commercial prospects were limited on two grounds – to keep a new antibiotic active against resistant strains reserved in case of treatment failures (so-called antibiotic stewardship), but also because of the muscle toxicity at higher doses. Indeed, Cubicin struggled to achieve blockbuster status and was only able to achieve it in 2014 by virtue of price increases. Cubist's challenges with Cubicin were also due to the many cheaper antimicrobial agents that could be used as first-line treatments for skin infections. Cubicin would typically only be considered after those generic first-line agents failed (due to resistance) in a consequently smaller number of patients. Nevertheless, Cubist was acquired by Merck & Co in 2015 for \$9.5bn including debt about a year before Cubicin went generic.

A number of learning points can be derived from recent antimicrobial commercial experience:

- Even novel antibiotics will face commercial challenges if they are approved for an existing indication where other generic antibiotics are widely used and approved.
- Indication-specific antimicrobial development has been thought by investors and analysts to be a restriction on the commercialisation of antibiotics. However, if the antimicrobial agent is novel



and no other agent has ever been approved for the indication, this combination may have a much higher chance of commercial success.

- Reservation or antibiotic stewardship to the labelled indication then becomes irrelevant.
- All recently developed antibiotics have been for the treatment of acute infections, where doubts on the commercial business case remain. More success has been achieved by new antibiotics that have been approved for chronic indications (like cystic fibrosis) or for preventative indications (like Destiny's first two products).

These challenges are echoed by the most recently developed antibiotics: retapamulin (developed by GlaxoSmithKline (GSK) and commercially unsuccessful), fidaxomicin (developed by Optimer, commercially unsuccessful, resulting in a take-under by Cubist), and dalbavancin (\$56m in sales FY17 and acquired by Activis for \$675m in 2014) and compared to Destiny's XF-73 in Exhibit 4 below.

#### Exhibit 4: Strategic commercialisation comparison for recently approved antibiotics and Destiny's XF-73

Antimicrobial agent	Indication	Competition
Cubicin (daptomycin)	Treatment of SSTIs & bacterial endocarditis	Many generic antibiotics, reserved for resistant infections
Altabax (Retapamulin)	Treatment of bacterial skin infections	Many generic antibiotics
Dificid (fidaxomicin)	Treatment of <i>C.difficile</i> -associated colitis	Generic vancomycin and metronidazole, and faecal transplants
Dalvance (dalbavancin)	Treatment of acute bacterial skin & skin structure infections	Many generic antibiotics, reserved for resistant infections
XF-73	Prevention of Staphylococcal post-surgical infections	No on-label competition, one branded off-label competitor (Bactroban Nasal), which is reserved for MRSA outbreaks and is associated with resistance.

Source: Edison Investment Research

Following discussions with the FDA, Destiny Pharma's lead product is expected to report the results of the US Phase IIb study in Q419 for the prevention of *Staphylococcal* post-surgical infections in high-risk patients. No antimicrobial agent has been approved for this indication previously, although there is some off-label use of one branded product (*Bactroban Nasal*; mupirocin calcium). This off-label use has been accompanied by significant concerns for the reduced utility of the agents in its clinically valuable, on-label, acute indication because the widespread preventative use in the many thousands of high-risk surgical procedures could further promote resistance selection. For abdominal surgery, where there is a significant risk of bowel perforation and the release of bacteria into the body cavity, surgical protocols to provide broad antimicrobial cover exist, and include *i.v.* vancomycin, although it has never been approved for this indication. This acceptance of post-surgical site infection prevention and its inclusion in some surgical guidelines, albeit for a different, much less clean surgical indication, should be important for acceptance by surgeons and payers of the prevention of post-surgical infection site indication. XF-73 has not been associated with the development of bacterial resistance in passage or clinical studies to date, nor has any pre-existing resistance been detected. XF-73 is also unique as it is not yet being studied in any other therapeutic indication and this profile is ideal for this indication.

### Destiny's answer: The XF series of antimicrobial agents in preventative indications

Destiny Pharma has discovered and is developing new classes of antimicrobial agents, which are intended to be initially indicated for the prevention of infections where efficacy relies on the *prima facie* absence of resistance. Destiny's XF series are bactericidal and have demonstrated preclinical and clinical activity against sensitive and resistant Gram-positive pathogens including MRSA and vancomycin-intermediate *S.aureus* (VISA). For preventive indications, this lack of resistance and bactericidal activity would be valuable in removing the ambiguity from empiric prescribing – the

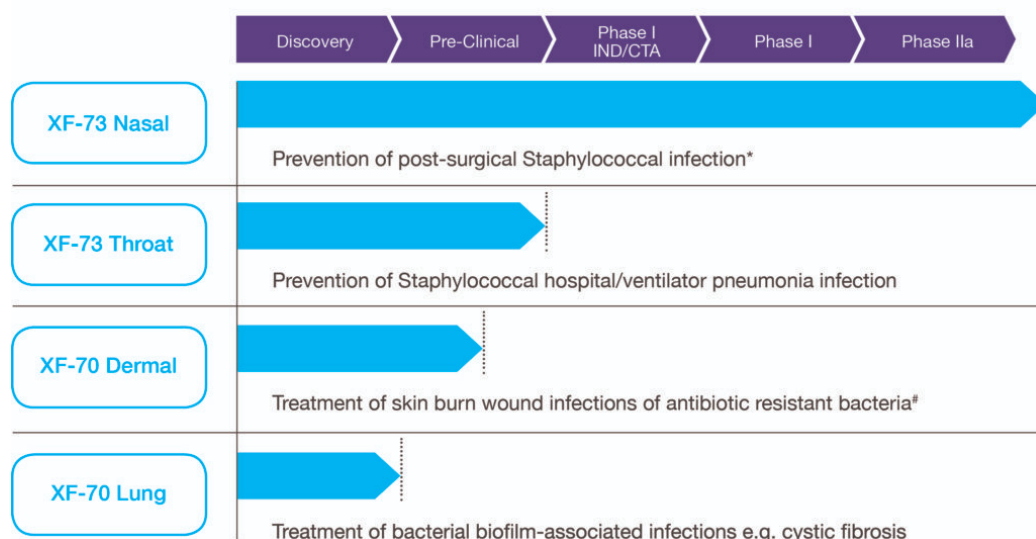
administration of an antibiotic without first determining the antimicrobial susceptibility of the infecting pathogen. In the same way as the XF series have broad-spectrum bactericidal Gram-positive activity, they appear to have a similar effect to the activity of the polymyxin antibiotic class against Gram-negative pathogens. Despite the introduction of the polymyxin antibiotic class in 1958, it remains largely active against Gram-negative resistant bacteria.

The porphyrin ring structure of the XF series (see Exhibit 1) contains a structure that has an affinity with the bacterial membrane and may be responsible for the release of the bacterial cytoplasm. The porphyrin ring has also enabled Destiny's second series of related drugs, which are much earlier in development but have photodynamic (light-activated) antibacterial activity in addition to the non-photodynamic, intrinsic antimicrobial activity of the XF series. The pipeline of Destiny's XF drugs is shown in Exhibit 5.

#### Exhibit 5: Destiny Pharma's XF series pipeline

##### XF Drug Platform

Potential Solution to Antibiotic Resistance



Source: Destiny Pharma. Note: \*New indication QIDP designated by FDA, October 2015, #Gram negative (*Acinetobacter baumannii* & *Pseudomonas aeruginosa*) and Gram positive (*Staphylococcus aureus*) bacteria.

## The prevention of post-surgical *Staphylococcal* infections

Destiny's lead product, XF-73, is in development for the prevention of *Staphylococcal* post-surgical site infections. XF-73 is a topical nasal ointment administered twice daily for between one and five days before surgery. The data underlying Exhibit 6 suggest significant antimicrobial activity after one day's dosing and this provides an attractive proposition of administration at the time of hospital admission. XF-73 has fast-track and QIDP status awarded by the FDA. *S.aureus* strains (including MRSA) are the most frequent cause of hospital infections and more than a third of surgical patients carry *S.aureus* asymptomatically in their noses, which can infect their own wounds, including surgical incisions. Published studies have shown that patients with *S.aureus* nasal colonisation have a tenfold greater risk of infection than non-carriers. About 85% of *S.aureus* strains infecting surgical wounds originate from the patient (so-called autoinfection). Other studies<sup>2,3</sup> have evaluated the extra cost of these post-surgical infections in US general surgical patients at \$20,785, 4.9 more days of hospital stay and 43.8 readmissions per 100 procedures. The latter cost is just as important as the others since US hospitals have to pay the costs of readmissions up to 30 days after hospital

<sup>2</sup> <https://www.ncbi.nlm.nih.gov/pubmed/29580355>

<sup>3</sup> <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5617700/>

discharge. It is therefore not surprising that hospital administrators and payers in general think of interventions that reduce post-surgical infections in terms of a return on investment.

## Clinical and non-clinical studies

The US IND for XF-73 in the prevention of *Staphylococcal* surgical infections was opened in February 2018, but was preceded by a significant amount of work, both inside and outside the US. XF-73 has been studied in a number of Phase I studies including the recently reported dermal sensitivity study, which enables the US clinical programme. Destiny also reported a 56-subject, US government-sponsored study (NCT02282605) where XF-73 vs placebo was shown to be safe and well tolerated, and demonstrated statistically significant nasal reduction of *S.aureus* after one day (see Exhibit 6). This effect was sustained throughout a five-day dosing period. The study provides Destiny with the option of a very short course, possibly at the time of hospital admission and then the day after surgery (as opposed to the five-day, off-label regimen of Bactroban Nasal prior to hospital admission).

**Exhibit 6: Demonstration of the rapid *S.aureus* nasal reduction of XF-73**

XF-73 nasal gel	Period (days)	p-value	Statistically significant (p<0.05)
2mg/g	1-5	p=0.0224	Yes
2mg/g	1-6	p=0.0128	Yes
2mg/g	1-14	p=0.0325	Yes

Source: Destiny Pharma

While the current US Phase IIb study, which will complete and report in 2019, is likely to have a microbiological endpoint, it will measure other data to assist the design of the registration studies. This will include the number and cost of post-surgical infections in both study arms, although we assume that Destiny will retain significant influence over the final design of the studies. XF-73 already has a significant advantage that (in addition to fast-track and QIDP status) in that it is expected to be the first product to be approved for the indication for prevention of *Staphylococcal* surgical infections. This means that clinically and microbiologically, XF-73 should only need to show superiority over placebo (although the actual primary and secondary outcome measures in Phase III are still to be agreed with the FDA) and then any subsequent competitors will need to show superiority over XF-73. There have previously only been two or three indications where a new drug has been required by the FDA to be tested against an unapproved control. It is highly unlikely that XF-73 would be studied against Bactroban Nasal in Phase III since the study would be virtually impossible to blind (different dosing schedules) and study sites would be resistant to using a valuable agent for the nasal decolonisation of MRSA in outbreaks in a large prevention study.

## Valuation

We have valued Destiny Pharma using a risk-adjusted NPV analysis, resulting in a valuation of £89.1m, or £2.04 per share based only on the use of XF-73 in the prevention of *Staphylococcal* post-surgical infections in high-risk surgical patients. We have assumed the first launch will be in the US, since this is where Destiny's subsequent clinical trials will be conducted, followed by other markets that include Europe (we have only included EU5), Japan (which has a history of extensive antibiotic use) and China (where Destiny already has an agreement with CMS). We have assumed that in the period after the Phase IIb results, which are expected at the end of 2019, Destiny licenses XF-73 on a global basis ex-China, although regional deals may occur. Our peak end-market sales estimations, and the valuation of the royalties and milestones from the sales of XF-73 are shown in Exhibit 7. Details of our milestone assumptions are shown in Exhibit 8. Our model also includes £0.5m in grant funding in FY19 since Destiny is in discussions with a number of grant funding bodies and antimicrobials are perceived to be a 'hot spot' for these incentives.

**Exhibit 7: rNPV valuation and XF-73 peak sales**

Product	Jurisdiction & price per course (\$)	Launch	Peak sales (\$m)	NPV (£m)	NPV/ share (£)	Probability	Licensing deal probability	rNPV (£m)	rNPV/ share (£)
XF-73	US - 450	2022	1,510						
XF-73	Japan - 400	2024	37						
XF-73	EU5 - 250	2023	321						
XF-73	China - 50	2024	3						
XF-73 royalties				336.9	7.7	35%	70%	65.2	1.5
XF-73 milestones				80.7	1.9	35%	70%	22.7	0.5
Unallocated costs				(15.5)	(0.4)	35%	100%	(15.5)	(0.4)
Net cash/(debt) at 31 Dec 2017				16.7	0.4	100%	100%	16.7	0.4
<b>Valuation</b>				<b>418.8</b>	<b>9.6</b>			<b>89.1</b>	<b>2.04</b>

Source: Edison Investment Research. Note: Number of shares = 43.56m. Net cash includes term deposits.

## Modest assumptions on XF-73

We have assumed that XF-73 will be initially confined to the indication for the prevention of post-operative *Staphylococcal* infection in high-risk patients. The preventative indication (to which the FDA has agreed) avoids the antimicrobial commercial issue of treating only infected patients with a short course therapy. Instead, the preventative indication covers a larger number of asymptomatic surgical patients. However, we have confined our model to some cardiovascular surgeries (not including interventional cardiology indications, for example), neurosurgical indications (with spinal injections and carpal tunnel release procedures excluded) and orthopaedic surgeries (excluding bunion surgery, knee arthroscopy and muscle, tendon, fascia 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 the other markets. As XF-73 is expected to complete and report the Phase IIb study in 2019, we have applied a 35% probability 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 conducted a sensitivity analysis (Exhibit 9, below). The effect of these base case assumptions on end-market sales of XF-73 is shown in Exhibit 7. The other key assumptions in our model include:

- Our US pricing of \$450 per course 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) since XF-73 will be the first drug approved in the prevention of post-surgical infections and, unlike Bactroban, will have a shorter course of administration and is not expected to be associated with the risk of treatment failures due to resistance.
- We have assumed that 90% of all high-risk surgical patients are prophylaxed with an antibiotic in all markets except China (10%), since the costs of a post-surgical infection in cardiovascular, neurosurgical or orthopaedic patients far outweigh the costs of prophylactically treating a large number of patients.
- We have conservatively assumed a 60% market share in all markets except China (where we have assumed 20%), even though there will be no on-label competition and XF-73 will not 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, we have assumed the licensing deal brings modest milestones that start at \$10m in 2019 and total \$190m, and a 10% royalty on net sales, as detailed in Exhibit 8.

**Exhibit 8: XF-73 milestone and royalty assumptions**

Milestone/royalty	Date	Rate/value (\$m)
Royalty rate	From 2022	10%
Collaboration agreement	2020	10
Phase III start	2020	5
NDA filing	2021	5
Approval/launch	2022	10
\$50m global sales hurdle	2023	10
\$100m global sales hurdle	2024	20
\$300m global sales hurdle	2026	30
\$500m global sales hurdle	2026	50
\$1bn global sales hurdle	2027	50
<b>Total milestone value (\$m)</b>		<b>190</b>

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 and dermal indications – the former is a smaller number of patients, but a higher value per patient – and other earlier-stage products that have *in vitro* activity against biofilms (Exhibit 5).

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 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. 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 9 may be an underestimation since it would apply to all antimicrobials – systemic and topical – and topical agents like XF-73 have far fewer toxicological issues. Exhibit 9 explores the sensitivity of the risk-adjusted valuation of Destiny Pharma to clinical trial probabilities at Phase II and the price per course of XF-73, with all other assumptions remaining unchanged.

**Exhibit 9: Sensitivity analysis of rNPV per share (£) of the XF-73 price per course vs clinical trial probability of success (%)**

Probability	US price per course (\$)				
	\$50	\$300	\$450	\$500	\$600
20%	0.52	1.00	1.29	1.38	1.57
35%	0.71	1.55	2.04	2.21	2.54
47%	0.86	1.98	2.65	2.88	3.32

Source: Edison Investment Research

The price of the drug will always be a key driver of valuation and, while off-label but branded Bactroban Nasal is priced at about \$300 per five-day course, we have assumed a price per course of \$450 for XF-73 because it is expected to be active against strains that are mupirocin-resistant, has a shorter course than Bactroban Nasal but, 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 iv vancomycin, which costs hospitals about \$50 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 ID physicians on the grounds that it promotes resistance. However, we have included \$50 as the bottom end of the pricing range in Exhibit 9. The prices in each market in

Exhibit 7 are linked to the US price of \$450 in our model so that when this changes in the sensitivity analysis in Exhibit 9, it feeds through to all jurisdictions in our model.

From the analysis in Exhibit 9, it appears that at a share price of less than £1.00 per share (the price around which Destiny is currently trading as a result of the recent weakness in UK biotech) the market is effectively assuming a price per course for XF-73 that is significantly below its only other branded, but unapproved competitor, which requires a longer treatment duration and is associated with resistance. In addition, if these attributes of XF-73 are recognised by payers (as resulting in a return on investment from fewer *Staphylococcal* post-surgical infections in high-risk patients), a higher price per course than our base case \$450 assumption could result in a significantly higher valuation.

## Financials

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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-2017 balance sheet showed cash and equivalents of £16.7m (including £5m in term deposits). The principal 2017 outlays were admin expenses of £2.5m (including £0.5m listing costs) and R&D costs of £0.8m, which we expect to increase as the US clinical programme progresses. This expenditure was softened by a £0.2m repayment relating to the R&D tax credit, which we also expect to increase in line with R&D spend. We anticipate R&D and administrative expenses combined increase to £6.8m in 2018 and £8.8m in 2019 before declining to £3.6m in 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 £0.5m in 2019. We have included placeholder funding of £7.8m (\$10m) in 2020 since we forecast that the funds raised in the 2017 IPO will allow operation until at least 2020, when we expect either the \$10m (assumed for the purpose of our model) licensing transaction for XF-73 or a fund-raising to provide funds to further develop Destiny's pipeline beyond 2020.



**Exhibit 10: Financial summary**

Accounts: IFRS, Year-end: December, £000s	2014	2015	2016	2017	2018e	2019e	2020e
<b>INCOME STATEMENT</b>							
Total revenues	0	0	0	0	0	500	0
Cost of sales	0	0	0	0	0	0	0
Gross profit	0	0	0	0	0	500	0
SG&A (expenses)	(441)	(482)	(505)	(1,011)	(2,100)	(1,900)	(1,700)
R&D costs	(1,090)	(274)	(496)	(387)	(4,700)	(6,900)	(1,900)
Other income/(expense)	(176)	(163)	(246)	(613)	0	0	0
Exceptionals and adjustments	(367)	(284)	(201)	(710)	(700)	(85)	(25)
Depreciation and amortisation	(0.8)	(0.8)	(1.3)	(2.1)	(2.2)	(2.3)	(2.3)
Reported EBIT	(2,076)	(1,205)	(1,450)	(3,222)	(7,502)	(8,387)	(3,627)
Finance income/(expense)	10.5	7.7	0.4	10.5	118.1	78.3	31.3
Reported PBT	(2,065)	(1,197)	(1,449)	(3,211)	(7,384)	(8,309)	(3,596)
Income tax expense (includes exceptionals)	303	182	192	234	1,100	1,600	500
Reported net income	(1,762)	(1,015)	(1,258)	(2,977)	(6,284)	(6,709)	(3,096)
Basic average number of shares, m	62	62	62	35,254	43,563	43,563	43,563
Basic EPS (p)	(5.52)	(3.18)	(3.94)	(8.45)	(14.43)	(15.40)	(7.11)
<b>BALANCE SHEET</b>							
Property, plant and equipment	0.6	2.5	1.2	22.3	20.5	18.7	16.9
Goodwill	0	0	0	0	0	0	0
Intangible assets	0	0	0	0	0	0	0
Other non-current assets	0	0	0	0	0	0	0
Total non-current assets	0.6	2.5	1.2	22.3	20.5	18.7	16.9
Cash and equivalents	2,004	1,119	1,481	11,724	6,091	(556)	4,278
Other financial assets (Term Deposits)	0	0	0	5,000	5,000	5,000	5,000
Inventories	0	0	0	0	0	0	0
Trade and other receivables	397	201	217	277	388	466	277
Other current assets	28	23	0	60	60	60	60
Total current assets	2,429	1,343	1,698	17,061	11,593	4,959	9,615
Non-current loans and borrowings	0	0	0	0	0	0	7,828
Other non-current liabilities	0	0	0	0	0	0	0
Total non-current liabilities	0	0	0	0	0	0	7,828
Trade and other payables	302	39	58	152	212	255	152
Current loans and borrowings	0	0	0	0	0	0	0
Other current liabilities	156	55	97	246	246	246	246
Total current liabilities	458	94	155	397	458	501	397
Equity attributable to company	1,972	1,251	1,544	16,686	11,101	4,478	1,406
Non-controlling interest	0	0	0	0	0	0	0
<b>CASH FLOW STATEMENT</b>							
Profit for the year	(2,065)	(1,197)	(1,449)	(3,211)	(7,384)	(8,309)	(3,596)
Taxation expenses	0	0	0	0	0	0	0
Profit before tax	(2,065)	(1,197)	(1,449)	(3,211)	(7,384)	(8,309)	(3,596)
Net finance expenses	(11)	(8)	(0)	(10)	(118)	(78)	(31)
EBIT	(2,076)	(1,205)	(1,450)	(3,222)	(7,502)	(8,387)	(3,627)
Depreciation and amortisation	0.8	0.8	1.3	2.1	2.2	2.3	2.3
Share based payments	367	284	201	710	700	85	25
Other adjustments	0	0	0	0	0	0	0
Movements in working capital	(150)	(163)	78	165	(50)	(35)	85
Interest paid/received	0	0	0	0	0	0	0
Income taxes paid	303	182	182	192	1,100	1,600	500
Cash from operations (CFO)	(1,554)	(901)	(988)	(2,153)	(5,750)	(6,735)	(3,015)
Capex	(0.8)	(2.7)	0	(23.2)	(0.4)	(0.5)	(0.5)
Acquisitions & disposals net	0	0	0	0	0	0	0
Other investing activities	11	8	0	(4,990)	118	78	31
Cash used in investing activities (CFIA)	9.7	5.1	0.4	(5,013)	117.6	77.8	30.8
Net proceeds from issue of shares	3,011	10	1,351	17,409	0	0	0
Movements in debt	0	0	0	0	0	0	7,828
Dividends paid	0	0	0	0	0	0	0
Other financing activities	0	0	0	0	0	0	0
Cash from financing activities (CFF)	3,011	10	1,351	17,409	0	0	7,828
Currency translation differences and other	0	0	0	0	0	0	0
Increase/(decrease) in cash and equivalents	1,467	(885)	363	10,243	(5,633)	(6,657)	4,844
Currency translation differences and other	0	0	0	0	0	0	0
Cash and equivalents at end of period	2,004	1,119	1,481	11,724	6,091	(566)	4,278
Net (debt)/cash (includes Term Deposits)	2,004	1,119	1,481	16,724	11,091	4,434	1,450
Movement in net (debt) cash over period	2,004	(885)	363	15,243	(5,633)	(6,657)	(2,984)

Source: Company 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 <a href="https://www.destinypharma.com/">https://www.destinypharma.com/</a>	N/A
Management team	
<b>CEO: Neil Clark</b> <p>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.</p>	<b>CSO: Dr William Love</b> <p>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&amp;D from discovery and lead identification, through preclinical development to Phase I/II clinical development in the UK, EU and US.</p>
<b>CFO: Simon Sacerdoti</b> <p>Simon qualified as a chartered accountant in 1997 with Levy Gee (now part of RSM), and subsequently spent time in the corporate finance teams at BDO and Ernst &amp; Young, advising public and private clients on a wide variety of UK and international transactions from fund-raising through to exits. In 2007, he joined Dowgate Financial Advisers, a small-cap corporate finance boutique, which specialised in AIM-listed companies. In 2009, he became one of the four founding partners and AIM-qualified executives of Cairn Financial Advisers. Simon is also one of the founders and until 2015 was CFO/COO of an innovative payments start-up, WeSwap.</p>	
Principal shareholders	(%)
William Love	15.8
Wade family	13.7
Canaccord Genuity Group Inc	10.2
Rosetta Capital V LP	7.1
Eagle, J.	5.2
A&B HK Co Ltd	4.4
CMS Medical Venture Investment	4.4
Companies named in this report	
Cubist Pharmaceuticals (CBST), Merck & Co. (MRK), GlaxoSmithKline (GSK.L), Optimer Pharmaceuticals (OPTR), Durata Therapeutics (DRTX), Vicuron Pharmaceuticals (MICU), Actavis (AGN)	

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