# Destiny Pharma plc

## M3: another gem in the portfolio

4 May 2021

**With the recent announcement of the positive Phase 2b clinical study of XF-73 in the prevention of post-surgical staphylococcal infections, Destiny has become a rare UK biotech company owning two Phase 3-ready assets. Yet NTCD-M3 may have been forgotten by investors with the excitement surrounding the positive clinical trial announcement. Indeed, the recent IPO of a NASDAQ-listed company with a similar asset to M3 highlights not just Destiny's superior asset quality, but also the valuation discrepancies between US and UK biotech companies that possess similar products.**

### NTCD-M3, a reminder

Destiny acquired the worldwide rights to the non-toxigenic *Clostridioides difficile* strain M3 (NTCD-M3) for the prevention of *C.difficile* infections (CDIs) in November 2020. The associated £10.4m gross fundraising was completed to enable the acquisition of the asset, and fund the preparation for the required Phase 3 clinical trial, which is expected to start in H2 2022. Despite a number of old antibiotic therapies, **CDIs remain an unmet, and potentially fatal medical need**. Broad-spectrum antibiotic use can result in the overgrowth of toxigenic *C.difficile* strains in the lower bowel and the detrimental effects of the toxin on the lower gastrointestinal tract inducing severe diarrhoea. The narrow-spectrum antibiotic treatment of CDIs often leads to recurrences which increase in their severity. CDIs are the most common cause of health care-associated infection in US hospitals with recurrence occurring in 25% to 30% of patients.

### First above competitors

While other companies are developing products to address CDIs, our review of the profiles of the microbiome-directed competition – none of which have yet been approved – suggest that **Destiny's NTCD asset could be superior, and not just because of better efficacy**. In Destiny's recent FY 2020 results announcement, NTCD-M3 topped the list on its portfolio slide, just ahead of the XF-73, also a Phase 3-ready asset. The protocol for the single pivotal Phase 3 study of NTCD-M3 has already been agreed with the FDA, placing it ahead of XF-73 in Destiny's pipeline and therefore 'first amongst equals' internally. Externally, our analysis places NTCD-M3 **ahead of the competition** re CDIs in terms of preventing relapses in this indication, amongst other metrics.

### Valuation updated

Our financial forecasts were modestly adjusted for Destiny's recent FY 2020 results on April 14 to reflect its cash position. While other competitors to NTCD-M3 have higher market capitalisations, they are based in the US with its greater access to investors and capital.

**Our fair value of Destiny Pharma again changes slightly to £200.2m or 335p per share (from £214.0m or 357p per share) as we amend our £/$ rate to 1.39**

**Summary Financials**

| £'000s, y/e 31 December | 2017A | 2018A | 2019A | 2020E | 2021E |
|---|---|---|---|---|---|
| Revenues | | | | | |
| EBIT | -3,222 | -6.084 | -5,585 | -6,553 | -5,944 |
| Basic EPS (p) | -8.5 | -11.9 | -10.8 | -12.0 | -8.4 |
| Net Assets | 16,686 | 12,257 | 7,759 | 12,436 | 7,425 |
| Net Cash | 16,724 | 12,061 | 7,480 | 9,744 | 5,056* |

*Source: Company historic data, ED estimates. *Including illustrative debt simulating a $10m up licensing payment*

**Company Data**

| | |
|---|---|
| EPIC | DEST |
| Price (last close) | 145p |
| 52 weeks Hi/Lo | 180p / 29p |
| Market cap | £87m |
| ED Fair Value - per share | £200.2m 335p |
| Net cash FY'20 | £9.7m |
| Avg. daily volume | 108,447 |

**Share Price, p**


*Source: ADVFN*

**Description**

Destiny Pharma (Destiny) is a clinical development-stage biotechnology company developing novel anti-infectives to prevent and treat infections caused by sensitive and resistant bacteria and viruses.

Destiny's proprietary drug discovery platform has generated a number of active antimicrobials including its lead drug XF-73. XF-73 has successfully completed a Phase 2b clinical study under a US IND for the prevention of staphylococcal post-operative infections. In September 2020, Destiny started a preclinical collaboration to prevent COVID-19 diseases by stimulating innate immunity. In November 2020, Destiny acquired the Phase 3-ready asset NTCD strain M3 for the prevention of *C.difficile* infections (CDI).

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## NTCD-M3

Destiny Pharma acquired NTCD-M3 in November 2020, raising £10.4m gross to buy the asset and to complete preparations, including scaling up the manufacturing of the NTCD-M3 bacterial spore, to be ready to start the Phase 3 study in mid-2022. The M3 product contains a naturally-occurring single strain of *C.difficile* that does not produce enterotoxin because its lacks the toxin-encoding genes and has been shown in human and animal studies to prevent CDI. CDI is a classic example of disease associated with a disruption of the human microbiome.

Even toxigenic strains are present in healthy patients' lower bowel flora but are kept in check by the many other thousands of microbial species that out-compete them for nutrients. In the event that this balanced normal flora, microbiome or hostile environment for toxigenic *C.difficile* overgrowth is disrupted, for example in patients treated with broad-spectrum antibiotics, the more hardy *C.difficile* strains that are normally present in low numbers in the GI tract, are gifted enough ecological space to overgrow, produce toxin and therefore disease. CDI has been linked to 29,000 US deaths each year and is more likely to occur in elderly hospitalised patients.

A number of companies are developing microbiome biological products extracted from modified faecal matter to treat CDI although, we believe that Destiny's NTCD-M3 strain has a number of key advantages, including safety and efficacy. The first-line treatment for CDI is usually a generic antibiotic – typically oral vancomycin and less so metronidazole because of the latter's higher recurrence rate – as the vegetive forms of *C.difficile* are usually sensitive to these agents. But the largely inert and very hardy spore forms can survive and, as soon as the antibiotic course is finished, are able to overgrow in the ecological space that is left. This results in a CDI first infection or recurrence. For multiple recurrences, outside the US, a largely undefined mix of 'normal' bowel flora is used as faecal microbiota transplantations (FMTs) are sometimes used to fill the ecological space before toxigenic *C.difficile* strains can overgrow. In the US, the FDA has concerns on FMTs, probably because of their undefined nature and potential to include other gastrointestinal pathogens such a superbugs like toxigenic *E.coli*, MRSA or even COVID-19.

NTCD-M3 is a single strain of *C.difficile* whose only variable in the room temperature-stable drug product is the number of spores. This should make regulators like the FDA very comfortable with NTCD-M3 as an easily defined product being at the opposite end of the defined biological product spectrum than FMTs. Between NTCD-M3 and FMTs lie other products that have been in clinical trials such as the 50 species of *Firmicutes* spores derived from the stool specimens of healthy volunteers in SER-109 from Seres Therapeutics, or CP101 from Finch Therapeutics which is an even less defined consortium, or mixed community isolated from healthy human donors.

**In NTCD-M3's case, the definition of the active product as a single bacterial spore which has been accurately tracked by genotyping, manufacturing, analysis and quality control is likely to be much easier, cheaper to manufacture, and has been-accepted by the FDA in the widest CDI population.**

**This contrasts with products comprised of complicated mixtures of bacteria. Indeed, the company believes they are the most advanced in developing the world's only single strain biotherapeutic treatment.**

## The microbiome as an active area of research

As the beneficial role of normal human commensal flora has become appreciated, so the microbiome has become an active area of research that is even being extended to optimising the response to certain cancer therapies. The first microbiome dysfunction to be addressed as a potential therapeutic intervention has been CDIs.

The company that has led the way in this field has been Seres Therapeutics, Inc., although its clinical program and completion of an IPO at a previous 2015 all-time high for the NASDAQ Biotech Index have

not been without their challenges. Between its positive Phase 1b, and after its failed Phase 2 ECOSPOR study results in 2016, not just Seres, but the whole microbiome research area moved from the spotlight to be under a cloud.

Seres compared the data from its Phase 1b and Phase 2 studies and modified the design of the Phase 3 ECOSPOR III study for the dose of the product and the screening of patients. The positive ECOSPOR III study results were announced in August 2020 and Seres is expected to file for FDA approval of its SER-109 product after its 225-patient open-label extension study ECOSPORIV – required because the ECOSPOR III study did not provide a large enough safety database for approval – reports.

So, while complex microbiome therapies for CDI have been rejuvenated by Seres' clinical trial success, single strain interventions like NTCD-M3 are at an earlier stage, and in other indications such as bacterial vaginosis, dermatology and oncology indications at public and private companies. In CDI, therapies of multi-strain or consortia products, like SER-109 from Seres, seem to be the first-generation of products.

## Competitors to M3

All the competitors to Destiny's single-strain M3 product are multi-microorganism products that range from an eight-microorganism consortium, to a highly complex seed microbiome community that will always be more difficult and more expensive to manufacture than the single strain M3 product. In addition, a single microorganism product, known to be naturally-occurring, where the genes for toxin production are deleted, is likely to have safety advantages over the competitors that are complex communities and have been derived from volunteers. This is not because the multiple organism competitors to Destiny's M3 strain are likely to contain toxigenic *C.difficile* strains – these should be easy to screen for and these screens are in fact, used to detect recurrences. But complex microbial consortia products derived from apparently healthy volunteers could contain other pathogens unless each is specified and tested for in the release specifications of each product. These pathogens may include common gastrointestinal pathogens such as toxigenic *E.coli* strains, *Salmonella* and *Shigella* strains and even COVID-19 (which is detected in higher numbers in waste water during outbreaks).

In terms of the time to a regulatory approval, Seres, with SER-109 having completed a single Phase 3 study may be the closest depending on when its open-label extension study reads out. Destiny's M3 appears in second place with a single Phase 3 study expected to start in H2 2022. Seres's product however, by the nature of its clinical trial revisions between Phase 2 and Phase 3, is intended for a much narrower orphan indication and population (patients with a history of three or more CDI recurrences in 9 months, with a positive *C.difficile* toxin test on the last recurrence and prior to treatment). This contrasts M3 which is intended for the prevention of a first CDI recurrence, and on the first CDI recurrence.

Recent US IPO Finch Therapeutics Group, Inc. has completed a Phase 2 study which it described as pivotal, but also as supporting data for the approval of CP101. Like Seres, Finch is also conducting an open-label 70 patient Phase 2 extension study, but it is questionable whether these two studies will provide a large enough safety database for approval. Vedanta Biosciences is the only private company in our table of comparators and is still in a Phase 2 study with very little data published on its earlier clinical trials. Finch's complex microbiome seed product is likely to be the most expensive to manufacture as a pharmaceutical drug product because of the testing required to define the product and exclude the presence of pathogens.

Vedanta's product VE303 is closer to Destiny's M3 in the complexity spectrum, with FMTs at one end and M3 at the other. VE303 consists of a consortium of eight microbial species in a 'rationally-defined bacterial consortium' not isolated from healthy volunteers. While VE303 is a step in the right direction for a defined drug product, it is eight times as complex as M3. CP101 and SER-109 are much more complex mixtures of bacteria, or bacterial spores isolated from healthy volunteers and their manufacturing and cost of goods is likely to be more complicated and more expensive, respectively, than Destiny's M3.

**Comparison of NTCD-M3 and its competitors**

| Product | Administration & dose duration | # Spores, Dosage form | Duration of study (weeks) | # Patients in latest study | Prior bowel prep / antibiotics required | Recurrence rate (placebo) p-value |
|---|---|---|---|---|---|---|
| **NTCD-M3 (Destiny)** | Oral for 7 days | $1x10^7$ dry powder | 6 | 157 (1:1:1:1) | N / Y | 5% (30%) p=0.01 |
| CP101 (Finch) | Oral, for 1 day | $6x10^{11}$ dry powder | 8 | 206 (1:1) | N / Y | 25.5% (38.5%) p<0.05 |
| SER-109 (Seres) | Oral for 3 days | $1.7x10^9$ Frozen | 8 | 182 (1:1) | Y / Y | 11.1% (41.3%) p<0.001[1] |
| VE303 (Vedanta) | Oral for 14 days | Up to $1.1x10^{11}$ Dry powder | 8 | 146 (1:1:1) | N / Y | Not yet known |

*Source: Company data, various websites* *[1]12-week data from an October 2020 conference presentation*

Seres' SER-109 has the added complication that its complex bacterial consortium is supplied as frozen cultures derived from FMTs which will have **a very short shelf-life** compared to the other dry or lyophilised products. Destiny's dry powder capsules extend this theme further by having extended room temperature stability.

The only real area where a competitor to M3 has an advantage at the moment is Finch's single-day dosing of CP101. This may not be a significant issue since CDI patients are likely to be hospitalised (or at least institutionalised) as their disease is monitored and dosing, whether on one, three, seven or fourteen, supervised by medical staff. The real determinant of product success, bearing in mind the 70% or greater relapse rate with antibiotics, is the efficacy of the product as measured by relapse rate. Single day dosing becomes rather academic if a clinical cure takes six to eight weeks of monitoring to determine.

## Clinical efficacy – The real kicker

In the Phase 2 study of M3, faecal colonisation increased from 63% to 71% with the higher dose ($10^7$ spores per day) of M3. CDI recurrence occurred in 30% of 43 placebo patients and in 11% of 125 M3-treated patients with the lowest 5% recurrence rate being observed in the 43 M3 patients treated at the highest ($10^7$ spores per day) dose. Although this best-case efficacy amongst microbiome products to treat CDI has only been observed in M3's Phase 2 study in a 43-patient subgroup treated at the highest dose, it is nevertheless **the high watermark of efficacy in this indication**, although there are some apples to pears comparisons in the different number of recurrences in the populations treated with the different products.

Perhaps this has been recognised in the views of the FDA who have agreed the design of a single Phase 3 study with Destiny that is due to start in H2 2022. The FDA have also approved Destiny's clinical trial protocol for M3 in the largest patient population of all its competitors – for the treatment of first CDI episode, and on first CDI recurrence – which would tend to confirm the FDA's view on the safety of a single-strain product in this larger patient population. For the less efficacious products from Seres and Finch, extension studies (a 70-patient Phase 2 study in Finch's case) remain underway and although these were probably demanded by the FDA on safety grounds, the recurrence rates will be included in the BLAs and could degrade efficacy further. For Vedanta, a single, placebo-controlled 146-patient Phase 2 study is ongoing.

**On the data that is known so far, M3 appears to have the best profile on the basis of the efficacy demonstrated, in addition to safety, manufacturing cost and complexity grounds.**

## Relative valuations

As two of Destiny's competitors are publicly listed, it might be thought that in an efficient and rational market the valuations of all three would, at least partially, reflect the value of their products to treat CDI recurrences.

Like Destiny, Seres and Finch have other products in their portfolios, at earlier stages behind their lead products for CDI recurrences. Unlike Destiny though, both Seres and Finch have partnerships with larger companies. Shortly after its IPO in 2015, Seres announced a license to its first four products with Nestle Health Science with a $120m upfront payment. In 2017 Finch announced a global collaboration to develop microbiome therapeutics for inflammatory bowel disease that included a $10m upfront payment.

In late April 2021 the market capitalisations of Seres and Finch were $2.0bn and $641m (£1.42bn and £462m, respectively) whereas Destiny's market capitalisation, with a more superior product, is **£87m**. Part of this differential is due to the partnering and validation of bigger companies and part is due to the greater appreciation of biotechnology, access to investors and capital, in the US market.

Private Vedanta have signed collaborations with Bristol Myers Squibb, Pfizer and Johnson & Johnson and although financial terms were not disclosed, Vedanta raised a Series C funding round in May 2019 raising $71m. By the listed comparisons at least, there appears to be a local valuation disconnect.

But although our risk-adjusted NPV valuation of £200m still looks somewhat of a bargain compared to the US listed comparators, we are not changing our basis of valuation at this point. Although announcement of a partnership on either M3 or XF-73 would almost certainly change that view.

## Consolidated Income Statement & Forecasts

| £'000s, y/e 31 December | 2017A | 2018A | 2019A | 2020A | 2021E |
|---|---|---|---|---|---|
| **IFRS Income Statement** | | | | | |
| Total revenue | | | | | |
| Administration expenses | -1011 | -1800 | -1887 | -1925 | -2100 |
| R&D | -387 | -3546 | -3800 | -4500 | -3816 |
| Other income (expense) | -613 | | 306 | 12 | |
| Share-base payments & exceptionals | -710 | -738 | -204 | -139 | -25 |
| Depreciation & amortisation | -2 | -4 | | | -2 |
| **Reported EBIT** | **-3222** | **-6084** | **-5585** | **-6553** | **-5944** |
| **Reported profit before tax** | **-3211** | **-6008** | **-5521** | **-6481** | **-5836** |
| Taxation | 234 | 841 | 813 | 1070 | 800 |
| **Reported Net income** | **-2977** | **-5167** | **-4708** | **-5411** | **-5036** |
| Basic EPS (p) | -8.45 | -11.86 | -10.75 | -11.97 | -8.42 |
| Diluted EPS (p) | -8.45 | -11.86 | -10.75 | -11.97 | -8.42 |

*Source: Company historic data, ED estimates*

## Consolidated Balance Sheet & Forecasts

| £'000s, at y/e 31 December | 2017A | 2018A | 2019A | 2020A | 2021E |
|---|---|---|---|---|---|
| **Assets** | | | | | |
| **Non-current assets** | | | | | |
| Tangible assets | 22 | 30 | 33 | 26 | 16 |
| Intangible assets | | | | 2261 | 2261 |
| Total non-current assets | 22 | 30 | 33 | 2280 | 2278 |
| **Current assets** | | | | | |
| Trade and other receivables | 277 | 931 | 911 | 1172 | 277 |
| Cash and equivalents | 11724 | 7061 | 7480 | 9744 | 12250 |
| Total current assets | 17061 | 13028 | 8525 | 11425 | 13036 |
| **Total assets** | 17083 | 13058 | 8557 | 13705 | 15313 |
| **Equity and liabilities** | | | | | |
| **Equity** | | | | | |
| Ordinary shares | 436 | 436 | 439 | 598 | 598 |
| Share Premium | 17292 | 17292 | 17296 | 27086 | 27111 |
| Retained earnings | -1042 | -5471 | -9976 | -15247 | -20284 |
| Equity attributable to the company | 16686 | 12257 | 7759 | 12436 | 7425 |
| Total equity | 16866 | 12257 | 7759 | 12436 | 7425 |
| **Current liabilities** | | | | | |
| Trade and other payables | 152 | 404 | 514 | 726 | 152 |
| Total current liabilities | 397 | 802 | 798 | 1268 | 694 |
| Total non-current liabilities | | | | | -7194* |
| **Total equity and liabilities** | 17083 | 13058 | 8557 | 13705 | 15313 |

*Source: Company historic data, ED estimates, * Illustrative debt representing a $10m upfront licensing transaction payment*

| Consolidated Cash Flow Statements & Forecasts | | | | | |
|---|---|---|---|---|---|
| **£'000s, y/e 31 December** | **2017A** | **2018A** | **2019A** | **2020E** | **2021E** |
| Profit before taxation | -3211 | -6008 | -5521 | -6481 | -5836 |
| Depreciation & amortisation | 2 | 10 | 18 | 17 | 2 |
| Share-based payments | 710 | 738 | 204 | 139 | 25 |
| Movements in working capital | 165 | 381 | -83 | 91 | 321 |
| Net cash generated by operating activities | -2153 | -4721 | -4631 | -5492 | -4795 |
| **Investing activities** | | | | | |
| CapEx on tangibles & intangibles | -23 | -18 | -21 | -2264 | |
| Other investing activities | -4990 | 76 | 5063 | 27 | 107 |
| Net cash used in investing activities | -5013 | 58 | 5043 | -2192 | 107 |
| **Financing activities** | | | | | |
| Proceeds from issue of shares | 17406 | | 7 | 9949 | |
| Movements in debt | | | | | 7194 |
| Net cash from financing activities | 17409 | | 7 | 9949 | 7194 |
| Cash & equivalents at beginning of year | 1481 | 11724 | 7061 | 7480 | 9744 |
| **Cash & equivalents at end of year** | **11724** | **7061** | **7480** | **9744** | **12250** |

*Source: Company historic data, ED estimates*

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