Mereo BioPharma

Raring to go in rare diseases

Mereo BioPharma has built a rich pipeline of four late-stage clinical assets as it focuses on becoming a rare disease, specialty pharmaceutical company. Its orphan disease products are BPS-804 for osteogenesis imperfecta (brittle bone disease), and MPH-966 for the treatment of alpha-1 antitrypsin deficiency (AATD). The strategy is to in-license more late-stage assets for the treatment of rare diseases. Two other programmes for larger indications have already generated compelling Phase II data. Mereo BioPharma aims to out-license these, with the first deal expected in 2019. We value the company, using an rNPV model, at £510m, or 615p a share (fully diluted).

<table>
<thead>
<tr>
<th>Year-end: December 31</th>
<th>2016</th>
<th>2017</th>
<th>2018E</th>
<th>2019E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sales (£m)</td>
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<td>0.0</td>
<td>0.0</td>
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<tr>
<td>Adj. PBT (£m)</td>
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<td>(43.3)</td>
<td>(32.2)</td>
<td>(30.7)</td>
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<td>Net Income (£m)</td>
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<td>(38.8)</td>
<td>(30.7)</td>
<td>(28.9)</td>
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<tr>
<td>Adj. EPS (p)</td>
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<td>(51.9)</td>
<td>(39.4)</td>
<td>(36.8)</td>
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<tr>
<td>Cash (£m)</td>
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<td>25.6</td>
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<td>EBITDA (£m)</td>
<td>(36.1)</td>
<td>(45.3)</td>
<td>(34.2)</td>
<td>(34.2)</td>
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</tbody>
</table>

Source: Trinity Delta; Adjusted numbers exclude share-based payments and exceptional.

- **Rich pipeline that is progressing well** Mereo BioPharma acquired three products from Novartis in 2015. Effective in-house expertise in bone and musculoskeletal, respiratory, and endocrine diseases has resulted in commendable execution of the development programmes. Impressive Phase II results have been reported for BGS-649 and BCT-197, and initial data from the Phase II trial in osteogenesis imperfecta (OI) with BPS804 is due in H119. MPH-966 was in-licensed from AstraZeneca in 2017 and the first patient in Phase II study in AATD should be treated in Q418.

- **Clear focus on rare diseases** Mereo BioPharma plans to commercialise BPS-804 in OI and MPH-966 in AATD itself, and to out-license BCT-197 (acute exacerbations in COPD) and BGS-649 (testosterone deficiency). Interest has already been shown in the latter programmes, especially BCT-197, which the company is optimistic about partnering as soon as 2019. The funds from any deal will be used to support the development of its rare disease assets, including additional in-licensed products.

- **BPS-804’s potential to become more apparent in 2019** Data from the Phase IIb trial in OI will give a better indication of BPS-804’s therapeutic potential. Results from the year-long study will be delivered throughout 2019, including the full data in Q419. It is also expected that the timing of the European pivotal trial and route to market in the US will become known over the period.

- **rNPV model suggests a valuation of 615p/share** We have employed a classic rNPV model to value Mereo BioPharma. Using conservative assumptions throughout, the current valuation is £510m, equivalent to 615p a share (fully diluted). The cash position of £36.9m at H118 should enable the company to operate through to late 2019. An F-1 form is filed with the SEC, leaving open the potential for a NASDAQ listing, which we view as a positive strategic and financial opportunity.

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**Company description**

Mereo BioPharma develops and commercialises innovative therapeutics addressing rare and specialty diseases. These are acquired or licensed in at clinical stages from large pharmaceutical companies. The portfolio consists of four compounds that are progressing through late clinical development.

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**Investment case**

Mereo BioPharma is a clinical-stage biopharmaceutical company focused on rare and speciality diseases; the smaller indications will be self-commercialised and the larger ones out-licensed. It was created in 2015 to exploit the opportunities that arise when large pharmaceutical and biotech companies rationalise their development portfolios or clinical programmes no longer fit strategic priorities. The maiden deal in 2015 saw Novartis take an equity stake (19.5% of the company) with a subscription agreement for additional shares in return for three clinical programmes addressing diverse niche indications. In 2017 a product candidate was licensed-in from AstraZeneca, with the option to acquire following results from a clinical trial. We believe the existing infrastructure can support between 5 and 7 clinical programmes.

Mereo BioPharma was listed on AIM in June 2016. Over £125m has been raised in equity since inception and it has a £20m debt facility with Silicon Valley Bank and Kreos Capital. The leading shareholders are Woodford Investment Management (41.9%) and Invesco Asset management (26.9%). In April 2018 management explored a listing on the NASDAQ exchange with the aim of raising investor and corporate awareness in North America. The company is based in London and has 31 full-time employees.

**Valuation**

We value Mereo BioPharma using an rNPV model of the four clinical programmes, which are then netted out against the cost of running the business and net cash. The success probabilities in each indication are based on standard industry criteria for each stage of the clinical development process, but flexed to reflect the data for the differing indications. We have employed conservative assumptions throughout; for example, erring on the cautious side for factors such as the timing of clinical studies, market launches, adoption curves, and patient penetration. Despite such a deliberately cautious approach we value Mereo BioPharma at £510m, equivalent to 615p per share (fully diluted).

**Financials**

Mereo BioPharma had net cash of £36.9m at H118, with a further £8.2m R&D tax credit for 2017 received in August; at the forecast cash burn this translates to a runway through to late-2019. The acquisition opportunities that are presenting themselves suggest that a strengthening of the capital base is warranted. This could be achieved, at least to a degree, by the successful out-licensing of the two assets, BGS-649 and BCT-197, that are not targeting rare diseases.

**Sensitivities**

Mereo BioPharma’s strategy deliberately targets programmes at the later clinical stages, eschewing earlier stage programmes completely, where the risk profile tends to be lower. However, albeit reduced, the typical industry risks associated with clinical trial results, navigating regulatory hurdles, ensuring sufficient financing is in place, partnering discussions and, eventually, pricing and commercialisation still apply. Our main sensitivities are detailed later (in the body of the note), with particular emphasis on each individual programme.
Mereo BioPharma: small but perfectly formed

Mereo BioPharma aims to develop and commercialise a portfolio of rare disease therapies, which have been acquired from larger drug players. Currently the portfolio consists of four programmes, two that target significant niche segments and two for Orphan Drug indications. The compelling Phase II data generated on the larger indications will be used to out-licence these programmes. The simplicity of the approach belies the strength and depth of in-house expertise in place to execute the strategy successfully. There are several value-inflection points approaching, both in terms of clinical results and corporate events. A planned US listing would, in our view, hasten progress in achieving the goal of becoming the partner of choice for such projects. We use a rNPV-based model, which yields a valuation of £510m, equivalent to 61.5p/share.

Acquiring niche clinical assets from large companies’ pipelines

Mereo BioPharma was created to exploit the opportunities that regularly present themselves as promising clinical programmes within an originator company are de-emphasised. The reason could be product related, for instance a failure to demonstrate the desired clinical profile in a commercially large and competitive therapeutic area, or it could merely be a change in research priorities as management (often new) refines its visions, goals, and objectives. Typically, such clinical assets have had significant effort expended and investment made, resulting in extensive supporting data packages and robust intellectual property; yet they now languish aimlessly within the originator’s development pipeline.

Creating a well-balanced and diversified product portfolio

The maiden deal was struck with Novartis in 2015 and covers three clinical assets that had fallen victim as Novartis reviewed its strategic direction. The programmes are: BPS-804, in Phase IIb for osteogenesis imperfecta; BGS-649, completing Phase IIb for hypogonadism in obese men; and BCT-197, which has completed Phase II to reduce acute exacerbations in COPD. In exchange Novartis received initially 3.85m shares for 19.5% of the equity, with a subscription agreement for additional shares. In 2017 MPH-966 was licenced-in from AstraZeneca; it is in Phase II for countering the damage caused by excess neutrophil elastase in α1-antitrypsin deficiency. The deal is structured such that MPH-966 can be acquired once its value is demonstrated by the trial data.

A deceptively simple approach that will be validated by trial data

Management’s intention is for Mereo BioPharma to become the natural partner for any originator company that is seeking to realise value from its non-core niche clinical assets. The operational structure is in place and its abilities, both in-house and through collaboration, are increasingly being recognised. Mereo BioPharma’s clear focus is now on in-licensing products for the treatment of rare diseases in respiratory, bone/musculo-skeletal or endocrine indications, with the aim of developing and marketing the products themselves.

The proposed NASDAQ listing could provide valuable access to funds and open up opportunities

The next 12 months should see a series of trial results that will help validate Mereo BioPharma’s approach. For us it is the simplicity and scalability of the concept that has such appeal. The potential US listing, on NASDAQ, is a natural next step as it allows not only greater access to funds for future deals when required but, notably in our view, helps raise the company’s profile in the important US market, and with a sizeable number of companies based there.
Commercially driven development

The concept underlying Mereo BioPharma's approach is straightforward and commendably simple. The larger pharmaceutical and biotech players have extensive development pipelines where, for any number of reasons, a particular programme may no longer be core to their strategic plans. This could be as:

- the larger pharmaceutical and biotech players periodically examine their strategic priorities; or
- as emerging data means a clinical profile is no longer deemed sufficiently competitive for the original, and more sizeable, indications; or
- it could be that a programme is not sufficiently commercially attractive against other programmes that are vying for limited funding budgets.

Whatever the reason, these programmes have usually had sizeable amounts, and much effort, devoted to them but are found to be left in limbo.

Mereo BioPharma was specifically created to exploit these opportunities. It has sufficient in-house expertise to identify and assess potential targets and, importantly, adequate resources to progress them rapidly once acquired. From the outset Mereo BioPharma formed close relationships with established CROs (Contract Research Organisation) to expedite its clinical plans. Specialist third-parties also assist in related areas, right from pre-acquisition evaluations to undertaking international multi-centre pivotal studies. This allows greater flexibility to deal with workloads, which are often periodic in nature, without requiring the additional resources to be a fixed element of the cost base.

Exhibit 1: Mereo BioPharma’s approach in a nutshell

- Identify promising drug candidates in the pipelines of pharmaceutical and large biotech players that are unfunded for strategic reasons;
- Ensure the right data package, with appropriate CMC and intellectual property, is in place and then secure the asset;
- Allocate sufficient resources to progress clinical trials to the next value inflection point, using in-house and external expertise;
- Prepare commercialisation plans: orphan and rare disease compounds for self-commercialisation (specialty to be partnered or out-licensed);
- Structure innovative deals that ensure all partners share in a programme’s success, create genuine “win-win” situations;
- Repeat the above five steps...

Source: Mereo BioPharma, Trinity Delta

The five stages of this approach are summarised in Exhibit 1, with the first being the most challenging. The identification of a suitable target candidate is based not simply on publicly available information but, inevitably, on a network of formal and informal industry connections. The goal is to find compounds where the clinical profile is no longer appropriate for the originator company but falls nicely into Mereo BioPharma’s sweet spot.

The ideal profile would be a compound that addresses an Orphan Drug indication or a rare disease for a respiratory, bone/musculo-skeletal, or endocrine indication.
Interested in rare disease assets in three therapeutic fields

Products for rare diseases can usually be commercialised through a small, targeted sales effort and more of the value is retained internally. Mereo BioPharma has also established a deep level of knowledge in the three therapeutic areas mentioned from its experience of developing the Novartis products. Two of the assets that were initially in-licensed are for specialty indications with a larger, but well-defined, commercial opportunities. These will be partnered for Phase III development and marketing, and the proceeds used to support the development of a broad portfolio of rare disease assets.

In all cases, Mereo BioPharma only selects products with a straightforward clinical trial pathway, with the proof-of-concept and pivotal trials being achievable with small, and relatively inexpensive, studies.

A balanced and diversified portfolio of late-stage programmes

The current portfolio consists of four clinical assets, three from the original deal with Novartis and the fourth licensed in from AstraZeneca (Exhibit 2). The portfolio is well diversified, with each of the product candidates employing a different mechanism of action and targeting a distinct indication. The risks have also been contained by selecting product candidates that have already generated positive clinical data for the target indication or for a related indication. Further risk mitigation is through selecting a mixture of drug candidates, with some having novel modes of action and others having proven safety and efficacy albeit in a different indication. Comprehensive details for the individual elements of the pipeline are provided in body of the note.

Exhibit 2: Mereo BioPharma pipeline summary – status and likely timings

<table>
<thead>
<tr>
<th>Product</th>
<th>Source</th>
<th>Indication</th>
<th>Timings</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPS-804 setrusumab</td>
<td>Novartis</td>
<td>Osteogenesis Imperfecta (OI)</td>
<td>Phase IIb Pivotal Phase IIb/III (paediatrics)</td>
</tr>
<tr>
<td>MPH-966 alvelestat</td>
<td>AstraZeneca</td>
<td>α1-antitrypsin deficiency</td>
<td>Phase II Proof-of-concept</td>
</tr>
<tr>
<td>BGS-649 leflutrozole</td>
<td>Novartis</td>
<td>Testosterone deficiency (HH)</td>
<td>Phase IIb extension study</td>
</tr>
<tr>
<td>BCT-197 acumapimod</td>
<td>Novartis</td>
<td>Exacerbations in COPD</td>
<td>Phase IIb dose finding</td>
</tr>
</tbody>
</table>

Source: Mereo BioPharma and Trinity Delta

The quality and depth of supporting data is invaluable

All the product candidates acquired have already received sizeable investment from their originator companies, and have substantial existing preclinical, clinical, and manufacturing data packages. Aside from the risk reduction aspects mentioned, the ready availability and quality of this data helps with the regulatory processes and any partnering or out-licensing activities. There is also a solid intellectual property estate attached to each product, with additional defences added as appropriate (for instance Orphan Drug status) and Mereo BioPharma has the global commercial rights to all the product candidates.

Extensive patents, but Orphan Drug exclusivity is most potent

Wide-ranging intellectual property protection in place

Mereo BioPharma has ensured that a comprehensive portfolio of patent families is in place. This not only arises from the original asset owner but, subsequent to purchase, additional patent applications have been filed wherever possible.
Currently there are around 350 issued patents, with a further 81 or so patents pending. The primary patents range in expiry dates from 2024 (MPH-966 for NE inhibition and BCT-197 composition of matter) to 2032 (BGS-649 in hypogonadism), however all four programmes may obtain Supplementary Protection Certificates (SPCs) or term extensions that add a further five years of protection. The expected dates of the primary protection and various additional marketing exclusivity periods is shown in Exhibit 3.

Arguably, the data and marketing exclusivity that is part of the Orphan Drug status inducements is an equally robust defence mechanism. The FDA Orphan Drug designation gives a number of advantages and incentives, including 7 years of market exclusivity. The EMA Orphan Drug designation is similar in concept although the conditions and incentives do differ, with the main one for our purposes being a marketing exclusivity period of 10 years. These exclusivities are enacted once the marketing authorisations are granted hence, unlike a typical patent protection period, a delay in a clinical programme does not erode the product’s market lifecycle. BPS-804 has been granted Orphan Drug status in both the US and Europe. MPH-966 is also eligible and Orphan Drug status for AATD will be applied for.

Exhibit 3: Key intellectual property portfolio

Source: Mereo BioPharma

All parties should gain if Mereo BioPharma is successful
The laudable aim is to create “win-win” situations. Whilst the rationale for value creation for Mereo Biopharma is easily understood, the originator company stands to benefit too. Such divestments of no longer core programmes allow for the immediate realisation of some of the embedded value that the assets have and, importantly, management is keen to structure deals that enable all parties to gain from any longer-term upside. For instance, the Novartis deal saw them take an equity stake and retain an interest including milestones and royalties on future commercial sales. Such an approach means any originator company seeking to streamline its portfolio is more likely to consider a well-structured proposal from Mereo BioPharma than simply divesting assets to the highest bidder.
Currently Mereo BioPharma has four programmes in its portfolio and the nature of the industry is that some will fall away and others will advance through to commercialisation. Realistically, the existing infrastructure is likely able to progress between five and seven programmes at any one time. Assuming a conservative rate of attrition, this suggests that management is actively exploring further product acquisitions. The Novartis and AstraZeneca precedents suggest that these may be either single assets or a suite of product opportunities. These also demonstrate management’s desire to minimise the upfront payments and only fully acquire the asset once further confirmatory data have been generated.

Overleaf we detail each of the four clinical programmes, and the expected newsflow associated with them is listed in Exhibit 4.

Exhibit 4: Mereo BioPharma catalyst calendar

<table>
<thead>
<tr>
<th>Date</th>
<th>Programme</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q418</td>
<td>MPH-966</td>
<td>Start of Phase II trial in AATD</td>
</tr>
<tr>
<td>Q418</td>
<td>BGS-649</td>
<td>12-month data from Phase IIb extension study in HH</td>
</tr>
<tr>
<td>Q119</td>
<td>BPS-804</td>
<td>Initial open-label six-month data from Phase IIb trial in OI</td>
</tr>
<tr>
<td>H219</td>
<td>MPH-966</td>
<td>Top line results of Phase II trial in AATD (potential exercise of option to acquire from AstraZeneca)</td>
</tr>
<tr>
<td>Q419</td>
<td>BPS-804</td>
<td>12-month dose ranging data from Phase IIb trial in OI</td>
</tr>
<tr>
<td>2019</td>
<td>BPS-804</td>
<td>Greater clarity on FDA views on Amgen's romosozumab BLA (read through for stance of cardiovascular risk of sclerostin inhibition); note that EU and Japan approval processes are progressing so may provide indication of other regulatory bodies’ risk perception.</td>
</tr>
<tr>
<td>2019</td>
<td>BCT-197</td>
<td>Progress on partnering discussions</td>
</tr>
<tr>
<td>2019</td>
<td>BPS-804</td>
<td>Initiation of pivotal paediatric Phase IIb/III trial (Europe and Canada) in OI</td>
</tr>
<tr>
<td>2019</td>
<td>BGS-649</td>
<td>Decision on timing of out-licensing (pre- or post-Phase III)</td>
</tr>
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</table>

Source: Trinity Delta, Mereo BioPharma  Note: OI = osteogenesis imperfecta; AATD = alpha-1 antitrypsin deficiency; HH = hypogonadotropic hypogonadism; BLA = biologics license application; COPD = chronic obstructive pulmonary disease
BPS-804: Targeting brittle bone disease

BPS-804, also known as setrusumab, is a fully humanised monoclonal antibody targeting sclerostin (SOST). Sclerostin is a protein secreted by the osteocyte cell (which is the cornerstone cell of bone structure) and that plays a pivotal role in bone homeostasis. Sclerostin was discovered to be the underlying mechanism of the high bone mass seen in two rare autosomal recessive diseases (sclerosteosis and Van Buchem disease). It is the deficiency in sclerostin that is associated with increased bone formation and decreased bone resorption. This led to the inhibition of sclerostin being explored as a novel therapeutic target for a variety of bone disorders, including large commercial indications such as osteoporosis and rare diseases like osteogenesis imperfecta.

The appeal of sclerostin inhibition lay in how it could not simply improve bone mass through reducing bone resorption (antiresorptive) but, importantly, through the activation of bone formation (osteanabolic). Other than parathyroid hormone (PTH) analogues, all current therapies for osteoporosis are antiresorptive. Reducing bone resorption, though helpful for the maintenance or improvement of bone strength, cannot replace the bone already lost and restore skeletal architecture. The promise of sclerostin inhibition meant that the optimal strategy of an initial anabolic treatment, followed by antiresorptive maintenance therapy, could be potentially achieved.

Three development programmes from major companies established a clear lead, with encouraging data in preclinical and early clinical osteoporosis studies that showed the ability of anti-sclerostin therapy to normalise bone mass and strength. The three programmes, in order of progression, were: Amgen’s romosozumab (AMG 785), Eli Lilly’s blosozumab (LY2541546), and Novartis’s setrusumab (BPS-804). Romosozumab progressed through initial Phase III studies smoothly (discussed in greater detail later); blosozumab hit material formulation difficulties despite positive Phase II results and was formally de-prioritised in 2015; and BPS-804 was a casualty of Novartis’s review of its strategic direction.

A promising data package was transferred across

Mereo BioPharma acquired BPS-804 as part of the original portfolio of three programmes from Novartis in 2015. It came with an extensive data package, including the requisite preclinical data and the results of four Phase I and II clinical trials in OI, HPP (hypophosphatasia) and osteoporosis. A 44-patient double-blind Phase II study in post-menopausal women with low bone mineral density was completed in 2013 and showed statistically significant improvements in bone formation biomarkers and bone mineral density, coupled with a clean safety profile. Before that, a small 14-patient open label Phase II study successfully examined the safety and pharmacodynamic profile of BPS-804 in adults with osteogenesis imperfecta. This also demonstrated statistically significant improvements in bone turn-over markers and bone mineral density. A similar 9-
Osteogenesis imperfecta is an orphan disease in need of therapy

Mereo BioPharma has focussed on developing BPS-804 for OI, which is better known as brittle bone disease, an orphan disease with different genotypes characterized by varying degrees of skeletal fragility. Most types (usually classified into eight categories) are caused by disruption or mutations of one or both of two genes (COL1A1 or COL1A2) that carry instructions for the production of type 1 collagen. Collagen is the major protein of bone and connective tissue including the skin, tendons, and sclera. The hallmark of OI is bone fractures that occur with only minimal to moderate trauma. Type I is the least severe form of the disease and is associated with relatively few fractures, whereas Type II is the most severe and causes babies to be born with multiple fractures and die within a few weeks of birth. Breaks can occur in any bone, but breakage of the lower limbs (often the femur) is the most common. In general, the earlier the fractures occur in life, the more severe the disease is.

On top of the clinical data from the small trial in OI conducted by Novartis with BPS-804, Mereo BioPharma has also shown in preclinical models of OI that BPS-804 increases bone mineral density (Exhibit 5).

Exhibit 5: Effect of BPS-804 treatment on bone density in Brtl (OI model) and WT (normal) mice bones

Comprehensive clinical programme in progress

In May 2017 Mereo BioPharma initiated a circa 100 adult OI patient, double-blind, placebo controlled Phase IIb clinical trial (ASTEROID) in the US, Europe and Canada. The patients are Type I, III, and IV with the defect in COL1A1/2 gene confirmed by genetic testing, and which account for c 80% of OI patients. Recruitment, despite the complex logistics (eg standardising transport for such delicate patients) to 27 specialist sites, is expected to complete before end-2018. There are three double-blinded, active arms, evaluating differing intravenous
doses (low, mid, and high), and one open-label arm at the top dose, which was initially the placebo arm before the study was amended in August 2018 to assist recruitment into the study.

The primary endpoint, measured at twelve months, is changes in trabecular volumetric bone mineral density (tvBMD) measured by high resolution peripheral quantitative CT (HRpQCT) and changes in bone strength on finite element analysis (FEA). Secondary endpoints include: tvBMD measured by HRpQCT at six months; BMD measured by traditional two-dimensional dual-energy X-ray absorptiometry (DXA); additional measures of bone parameters on HRpQCT; bone turnover markers and quality of life scores. The open-label study is expected to post its 26 week data in mid-H119 and 52 week data in mid-H219; the results from the whole study are expected in Q419.

Pivotal European Phase IIb/III trial in children set to start in 2019

A pivotal Phase IIb/III trial to support paediatric approval in Europe has been agreed and is planned to start in 2019. This European and Canadian study will treat c 160 children aged 5 to 18 with OI (Type I, III, and IV) who are currently on bisphosphonate therapy and use fracture rate at 12 months as the primary endpoint. Secondary endpoints will include trabecular volumetric BMD measured by HRpQCT, BMD measured by DXA, HRpQCT and bone turnover markers, and quality of life scores. The first 24 patients will enter a one month dose ranging element using three doses and a placebo arm, with all patients then moving to a 1:1 selected dose and placebo randomisation for the duration of the study. Positive outcomes would be expected to lead to a full marketing approval authorisation (MAA).

The trial could also lead to approval in adults

The study is also planned be used to validate the use of BMD measured by HRpQCT as a biomarker for bone fracture rates. This, in turn, could lead to the Conditional Marketing Authorisation (CMA) of BPS-804 in adults in Europe and Canada using data from the current Phase II trial and the proposed Phase IIb/III trial.

In the US the FDA has thwarted plans to include US centres in this pivotal Phase IIb/III trial in children so far, citing the possible cardiovascular safety concerns with sclerostin inhibitors that were likely flagged by romosozumab in the ARCH trial. Pending an expected rapid resolution of the issue, the clinical trial for BPS-804 in adults with OI in the US is still proceeding and there is the potential to include US sites into the planned paediatric study in the EU and Canada in due course.

Progress of sclerostin inhibitor class in US depends on FDA

As background, romosozumab (Amgen/UCB’s Evenity) is the first-in-class of the sclerostin inhibitors and is being evaluated as an anabolic bone former in osteoporosis. A Marketing Authorisation Application (MAA) was submitted to the European Medicines Agency (EMA) in January 2018, supported by three Phase III trials: FRAME including 7,180 postmenopausal women with osteoporosis; ARCH including 4,093 postmenopausal women with osteoporosis at high risk for fracture; and BRIDGE including 245 men with osteoporosis.

No notable cardiovascular safety signals were noted in FRAME or BRIDGE (arguably BRIDGE is too small a study to pick these up). In FRAME adjudicated cardiovascular events occurred in 1.2% of the women on romosozumab and 1.1% of those on placebo, with cardiovascular death rates of 0.5% and 0.4%
respectively. However, in ARCH the adjudicated cardiovascular events and stroke were 2.5% for romosozumab and 1.9% in the alendronate control arm, with cardiovascular death rates of 0.8% and 0.6% respectively. It is this difference in the ARCH groups that has raised question marks whether sclerostin inhibition could be associated with increased cardiovascular risk.

At the moment there is no definitive answer as to why there was such a disparity between the placebo-controlled FRAME study and the alendronate active control ARCH study. There is a school of thought\(^3\) that the difference could be accounted for through a cardio-protective effect seen with alendronate treatment but, as yet, that remains unproven. In July 2017 the FDA rejected Amgen’s Biologics Licence Application (BLA) for romosozumab, issuing a Complete Response Letter (CRL). In July 2018 the BLA was resubmitted with additional analysis of the data (with ARCH included) from the three Phase III studies. The results of the FDA’s deliberations are expected to become known over the coming six months.

Until the nature of the cardiovascular risk that has been observed is clarified an understandable cloud remains over the whole sclerostin class, irrespective of the overall risk/benefit profile. Having said that, it should be noted that the required clinical profile for a product in osteoporosis is quite different to that of a drug in OI; hence, BPS-804’s potential in OI in the US should not be dependent on if, and how, romosozumab is approved by the FDA for osteoporosis. Realistically, the FDA is unlikely to make a clear “approve” or “not approve” decision, with the most probable outcome being approval with a condition or warning on the product label. In the osteoporosis setting this may affect its clinical adoption (and hence commercial potential); however, in the OI setting the patient need is such that we consider the romosozumab outcome is unlikely to be an issue for BPS-804.

**A rare and debilitating disease with few treatment options**

Osteogenesis imperfecta (OI) is a debilitating disease for which there is currently no FDA or EMA approved treatment. Therapy is aimed at preventing and treating fractures, maintaining individual mobility, and striving to strengthen bones and the supporting muscles. Surgical procedures, such as rodling (the insertion of metal rods in the bones), have shown benefit but carry the risks associated with such major surgery. Medication typically involves the use of antiresorptives (off-label use) such as bisphosphonates to ameliorate bone mass. Other treatments used in osteoporosis have been evaluated clinically, but with limited reported results.

It is estimated that OI affects between 20,000 and 50,000 people in the US and between 32,000 and 51,000 people in the EU. The overall prevalence for all types of OI is estimated at between 5 to 7 per 100,000 individuals in the US and between 7 to 11 per 100,000 in Europe. OI is seen in both genders and all races. It ranges from severe (Type II) to mild (Type I); individuals with the most severe type may die at birth, whilst those with the mildest form may achieve a normal stature and life span. Types I and IV are the most common forms and are typically less severe; these tend to affect 4 to 5 per 100,000 people in the US and Europe. The

majority have a degree of physical impairment such as bowed arms and legs, short stature, curvature of the spine (scoliosis), and may be unable to walk unaided.

The commercial potential reflects the clinical need

In 2016 BPS-804 was granted Orphan Drug designation for OI in both the US (March) and Europe (June). Such designations offer a number of valuable benefits, such as assistance with filings and reduced fees, but the main incentive is a period of market exclusivity – 7 years in the US and 10 years in Europe. BPS-804 was accepted into the EMA’s adaptive pathways programme in February 2017 and admitted to the PRIME scheme in November 2017; these programmes reflect the desire to expedite approvals in Europe for novel drugs that address clear and pressing clinical needs.

The economic and social cost of OI is high. Not only are there the sizeable direct costs of treating the bone fractures, which are usually associated with a period of hospitalisation, but the available preventative treatments are typically expensive, notably the surgical options. In addition, there are material indirect costs such as the lost productivity of both the patient and care giver, as well quality of life and independence considerations such as mobility aids and home modifications. Against this background, the health economic and outcome data for BPS-804 should provide robust evidence to support its rapid adoption and reimbursement.

BPS-804 is an ideal candidate for self-commercialisation

The characteristics of the osteogenesis imperfecta (OI) market mean that it can be easily addressed through a small, well-targeted sales team. OI tends to be treated in specialist regional centres, staffed by knowledgeable and well-informed clinicians, with an equally enthusiastic and active network of patient support groups. Engagement with these communities will be straightforward if BPS-804’s efficacy and safety profile does match early indications. Clearly much depends on the FDA’s stance on the possible cardiovascular effects of the sclerostin class; however, we believe that Amgen/UCB have addressed the concerns posed by romosozumab’s ARCH study in their dossier re-submission.

In our modelling we have assumed that an approval submission could be made to the EMA in early 2022, based on the results generated by pivotal Phase Ib/III European and Canadian trial, with possible approval in late-2022 and the first significant sales in 2023. We have presumed US approval around a similar time, with the Phase IIb/III study expanded to include US centres. The actual route to market in the US will become clearer once there is greater visibility on the FDA’s views on romosozumab and data from the Phase II study has been published.

In terms of marketing assumptions, we forecast peak sales of $735m (£566m) with only modest penetration of the adult market. We estimate that BPS-804 will be used to treat c50% of the children with OI in the US and c40% in Europe, but only c20% of adults in both markets. This is because the clinical need for treatment is greater for children. We also estimate that the cost of treatment will be $90,000 per annum in the US and $60,000 in Europe; in line with our policy, this is conservative pricing for an orphan drug, and the final pricing will depend on the clinical benefit observed in the clinical trials.
**MPH-966: Addressing a respiratory rare disease**

MPH-966, previously AZD-9668 and also known as alvelestat, is an oral small molecule that selectively and reversibly inhibits neutrophil elastase (NE), an aggressive and cytotoxic protease enzyme that is associated with the destruction of lung tissue. NE has long been known to be implicated in the signs, symptoms, and disease progression in many lung disorders through its role in the inflammatory processes, mucus over-production, and lung tissue damage. Normally NE activity is tightly regulated by endogenous protease inhibitors including α1-antitrypsin (AAT), secretory leukoprotease inhibitor, and α2-macroglobulin. AstraZeneca initially developed alvelestat for the treatment of COPD, cystic fibrosis (CF) and bronchiectasis, where these NE pathways are known to be disrupted.

**AATD is relatively common but under-diagnosed**

MPH-966’s mechanism of action appears particularly well suited to negating the impacts of α1-antitrypsin deficiency (AATD). AATD is a relatively common inherited genetic disorder where the liver produces an abnormal version of the AAT protein or none at all. Depending on its composition, the rogue AAT can’t pass into the bloodstream and its accumulation in the liver can lead to damage, typically identified through the jaundice produced. Normally AAT plays a protective role in the lungs and it is the abnormal version’s unavailability, and hence lack of effective inhibitory activity, that can allow the destructive effects of NE to go unchecked.

The damage to the lungs is progressive, cumulative, and irreversible, with current therapy options limited to symptomatic treatments, such as inhaled steroids and bronchodilators, and prompt antibiotic treatment of chest infections. Smoking or exposure to tobacco smoke increases the risk of earlier lung-related symptoms and lung damage. In those with severe AATD, cigarette smoking can shorten life expectancy by as much as 20 years.

AATD has been identified in virtually all populations, but most commonly in individuals of Northern European (Scandinavian and British) and Iberian (Spanish and Portuguese) descent. In contrast, it is uncommon in populations with Asian ancestry. The severity of disease depends on the type of variations occurring on the SERPINA1 gene, with the most severe resulting in AAT serum levels that are around 15% of normal. Screening studies suggest 1 in every 1,700 to 5,000 people has an AATD genetic disposition (equivalent to a population of 145,000 to 425,000 in Europe); however, the number with severe AATD is estimated at around 60,000 in Europe and 50,000 in the US.

**The appeal is in countering NE over-activity in AATD**

Mereo BioPharma is developing MPH-966 for the treatment of severe AATD, where the inhibition of NE has the potential to protect AATD patients from further lung damage.

Mereo BioPharma licensed MPH-966 from AstraZeneca in October 2017 and has access to the existing comprehensive data package. Reflecting the impact out of balance NE has on three pulmonary diseases, these ranged from clinical studies in potentially large commercial indications, such as COPD (Chronic Obstructive Pulmonary Disease) and cystic fibrosis, as well as evaluations in bronchiectasis.
AstraZeneca has successfully completed 12 clinical trials with a total of 1,776 patients treated, showing that MPH-966 was safe and well tolerated.

**Mixed signals in prior clinical trials but promising signs**

Despite the clear scientific rationale, the trial programme found that, in general, a robust clinical efficacy was not demonstrated. For example, a 12-week Phase IIb COPD study, with 615 patients, examined adding MPH-966 (60mg bd orally) to inhaled budesonide and formoterol (Symbicort) maintenance therapy and found no meaningful improvement on lung function parameters and respiratory symptoms. Similarly, another 12-week Phase IIb COPD study, with 838 patients, explored adding MPH-966 (doses ranged from 5mg to 60mg bd orally) to inhaled tiotropium (Spiriva) maintenance therapy and showed no clinical benefit and no effect on biomarkers of inflammation or tissue degradation.

The results of a 38 patient, 4-week Phase II study in bronchiectasis (60mg bd orally) was more encouraging, with a significant increase in lung function and improvement in inflammatory markers. Equally, a 56-patient 4-week Phase II study in cystic fibrosis (60mg bd orally) showed mixed results, with no clear benefit on symptoms or lung function but promising trends indicative of effect. In both studies it was stated that, given the mechanism of action, longer term studies would be required to demonstrate efficacy. Also, it was noted that NE activity is higher in these indications than in COPD, so any benefit of MPH-966 in COPD would have been less marked and much slower to see.

**Proof-of-concept study planned to initiate in Q418**

In fairness, the treatment duration in these studies was probably too short for a disease-modifying treatment (4-week treatment in bronchiectasis and cystic fibrosis and 12-week in COPD patients) to expect significant changes in the primary clinical objectives. No studies have been performed to date in AATD but management believe the data generated in this trials programme demonstrated promising clinical benefit and biomarker evidence for AATD patients.

Mereo BioPharma is ready to initiate a proof-of-concept Phase II study in Q418. This is expected to involve around 165 severe AATD patients who have confirmed emphysema, declining FEV1, and have not undergone augmentation (or similar) therapy. The trial will last 12 weeks and consist of three arms (placebo and two MPH-966 doses); it will examine elastin breakdown and biomarkers of NE inhibition. Desmosine, a breakdown product of elastin that can be reliably and reproducibly measured and a good biomarker for lung damage, will be a primary end-point. Secondary end-points such as plasma Ao-Val\(^{360}\) (a validated biomarker of NE activity), NE levels in sputum, and a battery of lung function tests will also be included. The top-line results of this study, expected in H219, will guide the design of the pivotal Phase III trial.

Additionally, Mereo BioPharma is also supporting a number of investigator-led studies evaluating MPH-966 in treating AATD. An example is the team at University of Alabama (Birmingham, USA) which has been awarded a NCATS (National Center for Advancing Translational Sciences) grant, expected to total $10m, to study the efficacy and safety of MPH-966 in treating patients with AATD. Mereo BioPharma provides clinical trial material and regulatory support for the study.
The licensing/acquisition deal is structured to limit risks

Mereo BioPharma has structured the deal with AstraZeneca as a licensing agreement with an option for the outright acquisition of MPH-966. This allows the initial proof-concept Phase II study to be completed, using existing financial resources, and only if the outcome is positive would it be acquired at the already agreed price. The initial licence fee cost was $5m, of which $3m was paid in cash and the balance through the issuance of 490,798 new ordinary shares. Assuming all the development and regulatory milestones are achieved in a timely manner, the maximum payment to AstraZeneca would be $115.5m, payable through a combination of cash and new shares issued. No further details on the timings of the potential payments have been disclosed, but it is understood that a material payment will have to be paid to AstraZeneca in H120, if Mereo BioPharma decides to take MPH-966 into Phase III development.

Unspecified payments would also arise on the reaching of undisclosed commercial milestones. Royalties, ranging from high single digit to low double digit, would also be payable on a country by country basis for 10 years after launch or until patent expiry (whichever happens first). Understandably, AstraZeneca has retained rights to share in any unexpected upside. If MPH-966 were to be sub-licensed to a third party then a specified, but also undisclosed, percentage of the value would be payable to AstraZeneca.

Current treatments for AATD are limited

There are few genuine treatment options<sup>4</sup> for AATD, with the current focus being on managing the respiratory symptoms caused by the excess of NE. There are several approaches that aim to replace the faulty AAT, ranging from relatively basic replacement or augmentation therapy right through to gene therapy:

- **Grifols** is a leading plasma fractionator, based in Barcelona (Spain), with operations in Europe and North America. It has a long history in AATD and is the leading supplier of plasma-derived α1-antitrypsin infusion, branded as Prolastin-C. Although first introduced in 1988, a new ready-to-use liquid formulation has been introduced in many markets, with the US launch expected in H218.

- **CSL Behring** is a leading plasma fractionator, based in Pennsylvania (US), that has global infrastructure. CSL acquired Aventis Behring in 2004, which together with Nabi (US), combined to form CSL Plasma. Its product is branded as Respreeza in the EU and Zemaira in the US. This has been successfully evaluated in 180-patient placebo controlled trial, known as RAPID, that showed a significant, and sustained, reduction in lung tissue damage (as measured by CT scan).

- In 2010 the FDA approved Kamada’s Glassia, an α1-antitrypsin infusion, as a weekly treatment that aim to replace or supplement the missing AAT. The average annual treatment cost is around $80,000 to $100,000, which largely reflects the cost of manufacture through the fractionating of human plasma. Kamada posted Glassia revenues of $66m in 2017 and, through a distribution agreement with Shire, expects sales of around

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$237m in 2020. Kamada is believed to still be developing an inhaled version of its plasma-derived AAT, having completed a Phase II/III programme and is seeking a partner to progress to pivotal trials.

▪ Being an inherited genetic disorder AATD is a suitable candidate for gene therapy. Adverum Biotechnologies, a NASDAQ quoted US company, is progressing its lead programme, ADVM-043, through Phase I/II trials as a single-administration treatment to induce the long-term production of stable AAT protein. The attraction is that, once treated, the patient would continue to produce normal levels of the correct form of AAT. Clearly, gene therapy remains an experimental, and expensive, option.

A surgical option is lung volume reduction surgery, a technique where the least functional part of the lung is removed to improve the mechanics of breathing in the remaining part of the lungs. The aim is to reduce the initial lung volume by around 20% to 30%. The clinical data in AATD patients is limited but experience in non-AATD COPD is supportive. The obvious downsides are the risks and costs associated with such invasive surgery.

The most extreme solution is lung transplantation, but this should, in our view, only be considered under exceptional circumstances. Nonetheless, once the degree of lung damage has progressed beyond a certain point, this is the only option to prolong survival. It is worth highlighting that in all surgical options the original cause of the damage remains in place.

**MPH-966 is a clear candidate for self-commercialisation**

The nature of the AATD market mean that MPH-966 is well suited to being commercialised through a small, targeted sales team. Management intends to establish a marketing infrastructure in the US and Europe addressing the rare disease therapeutic segments and MPH-966 has the right characteristics for such an approach. We have assumed that a pivotal Phase III trial could start in 2020, with results in 2022 and a typical 12-month approval process, could lead to first marketing in 2023. We have modelled peak annual sales at $420m (£323m), with a 2024 launch date and a modest adoption profile, despite the attractive product features.
**BCT-197: Reducing exacerbations in COPD**

BCT-197, also known as acumapimod, is a small molecule, orally active inhibitor of p38 MAP (mitogen-activated protein) kinase. This is a key pathway in many chronic inflammatory states and has been studied extensively for conditions such as rheumatoid arthritis, Crohn's disease, asthma and COPD. Early development programmes failed due to poor efficacy and unacceptable side-effects, but a greater understanding of the complexities, and subtleties, of the p38 MAPK signalling mechanisms has allowed better targeting and more specific compounds to be developed. The challenge has been to inhibit the desired cytokines in the inflammatory cascade sufficiently to exhibit the necessary activity, but with the appropriate selectivity so as not to cause unwanted off-target effects.

**Acute exacerbations in COPD are a major medical concern**

The nature of inflammation in COPD is not straightforward. A number of inflammatory cells, including macrophages, neutrophils and T-cells, are involved and these in turn release a myriad of mediators that create a complex feedback loop that leads to chronic inflammation. Once established, a repeated cycle of repair and injury results in worsening structural remodelling of the airways walls (collagen deposition and mucus hypersecretion), alveolar enlargement, and emphysema. This downward spiral is punctuated by acute exacerbations, where the patient's condition worsens materially and, even once resolved, never returns to its pre-exacerbation status.

Acute exacerbations in COPD (AECOPD) are a major concern, both medically and economically. An AECOPD is defined as a sustained (24-48 hours) increase in cough, sputum production, and/or dyspnea. A frequent exacerbator will experience around two episodes of AECOPD per annum, with more than 10% requiring hospitalisation. The average duration is 7 to 12 days and its onset is often linked with an infection. AECOPD accounts for 13% of all acute hospitalisations, and contributes significantly to morbidity, death and quality of life issues. For context, COPD is the third largest cause of death in the US and the frequency and severity of exacerbations are among the principal factors that determine the prognosis. The 5-year survival rate for those experiencing three or more exacerbations per annum is 30%, whilst those without any have an 80% survival rate.

**BCT-197 being studied in Phase II trial**

The rationale for p38 MAP kinase inhibition in reducing acute exacerbations in COPD is well understood, with eight compounds having been evaluated clinically; its utility has been explored in sizeable development programmes by AstraZeneca (AZD-7624), GlaxoSmithKline (GSK-610677), Pfizer (PF-03715455), and Janssen (RV-568). The approaches have included both oral, where raised liver enzymes and incidences of rash were observed, and inhaled delivery, to gain higher local 5


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doses and improve the safety profiles. The animal data and results from early clinical studies has been very encouraging; however, most of the programmes have been discontinued or have stalled for a variety of reasons. It is worth noting the clinical effects appears to wane when used in a chronic setting (eg after 12 weeks) and that BCT-197 is currently being evaluated in an acute setting.

Novartis undertook a comprehensive early clinical evaluation, with BCT-197 the subject of three Phase I and two Phase II studies, involving a total of 498 treated patients, that showed a clean side-effect profile and promising anti-inflammatory activity. An exploratory Phase II trial examined 183 AECOPD patients in a four arm parallel format looking at one 20mg or one 75mg oral dose on Day 1 and one 20mg or one 75mg oral dose on Day 1 and Day 6 of the exacerbation episode. The results were presented at ATS 2017 (American Thoracic Society) in May 2017. Unsurprisingly, the two day regimen at the higher 75mg showed the best response, with a statistically significant improvement in FEV1. Dose-dependent improvements in markers for AECOPD were seen, as was a reduction in hospital stay, but statistical significance was not reached. No safety concerns were noted.

Positive outcomes from Phase II trial
The results and experience were used to design a larger Phase IIb study (AETHER) that Mereo BioPharma undertook. This involved 282 patients with two different dosing regimens (high and low dose) of three doses over five days versus placebo, on top of standard of care (including steroids, antibiotics, and bronchodilators), over a five day dosing period. Patients were then followed for 26 weeks. The primary endpoint was FEV1 (forced expiratory volume in one second), with a number of additional endpoints including hospital stay times, patient reported outcomes, recurrence rates of AECOPD and hospitalisations. It should be noted that these patients tend to already be on maximal bronchodilator therapy.

Top line data were reported in December 2017. The results showed a statistically significant improvement in FEV1 for both the low and high dose groups from baseline (p=0.012), although the difference over placebo was not significant.

There was also a significant reduction of more than 50% in clinical treatment failures (as defined by the number of re-hospitalisations for treatment of COPD) at days 90 through 150 in patients treated with the high dose of BCT-197 compared to the low dose or placebo (p≤0.027 to 0.05, Exhibit 6). Interestingly, the greatest impact with both low and high doses was seen in the severe exacerbation group (more than two exacerbations per annum), suggesting that the patient group with the greatest clinical need may benefit the most from BCT-197 treatment.

A potent anti-inflammatory effect was evident, with sustained reductions in inflammatory markers, fibrinogen and hsCRP (high-sensitivity C-reactive protein), seen in a dose-dependent manner. A significant reduction in the use of antibiotics and corticosteroids was seen in the follow-up phase of the study. There are currently two theories to explain BCT-197’s prolonged effect after such a short administration: the first is that it causes sensitisation to steroids; and the second is that a re-balancing of the neutrophil to lymphocyte ratio occurs.
Exhibit 6: Percentage of patients re-hospitalised for COPD following treatment for AECOPD with BCT-197 or standard-of-care/placebo

Source: Mereo BioPharma

Both dose groups also saw trends of improvements in other secondary endpoints but even though some didn’t reach statistical significance during the study duration. No safety concerns were raised, with no BCT-197 linked liver injuries and two cases of rash that resolved. An additional small drug-drug interaction study (DD) showed that BCT-197 had minimal impact on the Cytochrome P450 liver pathway, suggesting little need for dose adjustments in the target patient population.

Although the primary endpoint was FEV1, the more important data from a clinical and economic perspective is probably the reduction in treatment failure rate. Each exacerbation that a COPD patient suffers is generally associated with a long-term deterioration in their lung function and prognosis. There is also a significant economic cost linked with hospitalising a patient. So it will probably be this data which is of most interest to potential partners.

Product positioning attractive for the right partner

Management believes that BCT-197 offers these benefits over existing therapies:

- the potential to be a rapid-onset treatment targeting the inflammatory drivers of AECOPD;
- the ability to target anti-inflammatory response systemically and locally with easier oral administration than inhaled treatments;
- a simple oral regimen of three doses over five days that can be conveniently administered in either the hospital or an outpatient setting;
- it is designed to target pathophysiology of acute exacerbations without generalized immune suppression; and
- has the potential for efficacy in steroid-resistant population.

The nature of the COPD market, notably the expected size and duration of the clinical programme required for approvals in the US and Europe coupled with the marketing resources required for successful commercialisation, suggests that...
Mereo BioPharma will use the positive outcome of the AETHER study to seek an appropriate partner to progress BCT-197 further. The strength of data suggests a deal is likely to struck earlier rather than later, so we are modelling at the shorter end of the typical 12-18 months required to complete such transactions.

For our financial estimates, we have assumed that the remaining clinical programme for BCT-197 would be undertaken by a commercial partner. We have not factored any upfront element of the likely licensing deal, except in our valuation, in which we conservatively estimate the upfront payment will be $20m (£15.4m); we have forecast royalties of 10% of sales, net of the royalties due to Novartis, over the period of marketing exclusivity. The total milestone payments are estimates at c$100m (£77.0m).

The first marketing approval would depend on the nature and duration of the pivotal trial programme selected by the partner, but we have, cautiously, assumed the first launch would happen in 2023. Maintaining a cautious stance, we have forecast peak sales of $768m (£591m).

Conservative assumptions are used in our models for BCT-197
BGS-649: Holistic testosterone deficiency therapy

BGS-649, also known as leflutrozole, is an aromatase inhibitor being developed as a once-weekly oral treatment for hypogonadotropic hypogonadism (HH) in obese men. Aromatase inhibitors are used commonly to reduce tumour-driven oestrogen levels in hormone-sensitive breast cancers in women, but their mode of action lends itself to the treatment of other conditions where there is an imbalance between androgen and oestrogen activity. Novartis has a strong background in this area, having developed the blockbuster Femara (letrozole, now generic), and explored the follow-on compound, leflutrozole, in a variety of indications. The strategic review of its future therapeutic focus resulted in this programme, among several others, being de-emphasised.

HH appears to be well suited to aromatase inhibition

HH, or secondary hypogonadism, is due to insufficient levels of testosterone but, unlike primary hypogonadism (due to failure of the testes to produce enough), this is due to disruption of the hypothalamic-pituitary-testicular axis (HPT). The HPT pathway is a complex and essential endocrine pathway that plays a critical role in the regulation and activation of many bodily functions, notably the reproductive and immune systems. The effects of testosterone deficiency are wide ranging and include: reduced or loss of libido, erectile dysfunction, impaired sexual function, ejaculation disorders, fatigue, reduced physical endurance, lack of vitality, depression, loss of motivation, mood disturbance, and insulin resistance.

Oestradiol has an important effect on the regulation of testosterone biosynthesis and spermatogenesis. Most of the circulating oestradiol is derived primarily from the peripheral aromatization of testosterone by adipocytes located throughout the body. Obesity has a material influence as low testosterone can result in significant weight gain and the increased expression of aromatase in adipose tissue triggers the conversion of circulating testosterone (and other androgens) into oestradiol. Recent evidence suggests breaking this cycle can be highly effective and should become a primary goal in achieving clinical control.

It is in this obese HH patient group that a specific third-generation aromatase inhibitor has great appeal. BGS-649 is particularly well suited as its inhibition is not total and it preserves sufficient oestradiol to avoid potential side-effects, such as reducing bone mass, whilst only normalising testosterone levels. This contrasts with testosterone replacement therapy (TRT), where the risks of over-elevating testosterone levels remain important formulation and patient monitoring factors.

Encouraging safety and efficacy data from early trials

Novartis carried out a total of 8 clinical trials, of which two Phase II studies were for HH in obese men. The proof-of-concept Phase II study involved two parts, the first of which was an open-label, dose-ranging protocol with 14 patients using flexible dosing over a 12-week period. All patients saw their testosterone levels

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rise into the normal range (300 to 1,000ng/dl), with a mean of 514ng/dl from a mean baseline of 239ng/dl.

The second part was a double-blind, placebo controlled 12-week trial that planned to enrol 30 patients. Unfortunately, after 15 patients were enrolled, an error at a study centre saw three patients in the placebo arm mistakenly receive BGS-649 and the trial was terminated. The results in the treated patients saw the testosterone levels gain a statistically significant rise from a mean of 273ng/dl to 423ng/dl.

Notably, FSH (Follicle Stimulating Hormone) and LH (Luteinising Hormone) levels were increased without apparent disturbance of the physiological feedback mechanisms in the HPT axis. Both FSH and LH play key roles in sperm formation and LH plays a key role in endogenous testosterone formation and this may prove to be a key differentiating factor compared to existing TRT therapies.

Phase IIb results suggest an attractive activity profile
A Phase IIb study saw a total of 271 patients allocated into a four-arm (low-, intermediate-, high-dose, and placebo) double-blind protocol over 24 weeks with a 12 week follow-up. The study was performed in the US and Europe and top-line results were published in March 2018. The primary endpoint of normalising testosterone levels in over 75% of patients was met at all dose levels, with the secondary endpoint of achieving this normalisation in over 90% of patients met at the two higher levels (the lower dose was trending towards but failed to achieve statistical significance, Exhibit 7). All three doses also met the other secondary endpoints, including significant improvement in FSH and LH levels. Total sperm motility and levels of fatigue also improved. There was no overshoot in testosterone levels at any dose, so confirming that the normal feedback mechanisms remained undisturbed.

Exhibit 7: Change from baseline in testosterone following treatment with BGS-649

A six-month extension study, involving 143 men, is now underway to provide additional safety and efficacy data. The experience from the existing trials data, involving a total of 402 patients (both male and female), suggests a clean safety profile with no unexplained side-effects. The results are expected in Q418 and...
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will guide the future development programme. BGS-649 is not a programme that Mereo BioPharma would commercialise itself. The question really is whether it undertakes the pivotal Phase III trial itself and then seeks a partner or whether the partner is brought in earlier and shares in the last stages of development too.

**Differentiation will be key to success in a competitive market**

The incidence of obesity is rising across the globe, and with it the number of obese men with hypogonadotropic hypogonadism (HH). The World Health Organisation (WHO) estimates that 35.5% of adult males in the US are obese (the figure in Europe is lower at 21.9%) and that 15.8% of these suffer from HH. In actual numbers, this equates to around 7m men in the US and 5m in Europe who have HH that would benefit from treatment. However, all areas of testosterone deficiency are currently under-treated, with estimates that less than 13% of men are diagnosed and treated (the figure is thought to be lower in Europe, with only around 5% actively treated).

The market for the treatment of male hypogonadism is expected to reach $3.2bn in 2022 ([Allied Market Research](https://www.alliedmarketresearch.com)), a 3.1% CAGR, driven by an ageing population and a greater awareness of the associated conditions (notably obesity and Type II diabetes). The testosterone replacement market (TRT) accounts for more than half of the market but is expected to decline (−4.2% CAGR according to [Transparency Market Research](https://www.transparencymarketresearch.com)) as concerns over cardiovascular side-effects taint its image.

This remains a competitive segment, dominated by large players such as AbbVie ([Androgel](https://www.abbvie.com)), Allergan ([Androderm](https://www.allergan.com)), Eli Lilly ([Axiron](https://www.eli-lilly.com)), and Endo ([Fortesta](https://www.endo.com)), although smaller players have carved out sizeable niches by formulation or geography. The market growth is expected to be driven by newer, and more specific treatments, such as gonadotropin and gonadotropin-releasing hormones (GnRH). Against this market backdrop, BGS-649 appears well placed with an attractive and suitably differentiated efficacy and safety profile.

**Commercialisation strategy depends on the partner chosen**

The characteristics of the HH market mean that BGS-649 will most likely be marketed through a partner. The economics of any out-licensing agreement will need to consider whether it is better to have a large, multi-national player, or a smaller, specialised player. The larger company would have the appropriate marketing size and geographic reach, but BGS-649 would be effectively a portfolio in-fill. In contrast, a smaller, specialised player could be more motivated as BGS-649 would be a meaningful contributor to future growth.

For our modelling we have assumed that BGS-649 would complete the Phase III registration studies in early-2020, first regulatory submission in 2023, with a probable first approval, and launch, in 2024. BGS-649 has the clear potential to become a major blockbuster due to the rising levels of obesity in many countries, however most obese men are unaware that they have testosterone deficiency, and it is a competitive market. Thus, we have forecast relatively modest peak sales of $483m (£372m).
Sensitivities

In common with most innovative healthcare companies the three main sensitivities relate to the clinical and regulatory aspects, the execution of the commercialisation plans, and the financial resources required to accomplish these. More specifically, the key near- and medium-term sensitivities are directed to the clinical and partnering progress on the four clinical programmes:

- **BPS-804** is approaching a defining moment as a pivotal Phase IIb study in adults with osteogenesis imperfecta (OI) nears fruition and a similarly pivotal paediatric Phase IIb/III study in Europe and Canada is initiated. The outcome of the FDA’s review of Amgen’s romosozumab is a high profile determinant of the eventual commercial acceptance of sclerostin inhibitors as a class in osteoporosis; however, in our view, it is not likely to be a major factor in the more debilitating and poorly served OI setting.

- **MPH-966** will shortly start a proof-of-concept Phase II trial in patients with severe AATD. A positive outcome is a necessary prerequisite to continue development, but it can be appreciably difficult to demonstrate clinical significance in such respiratory disorders within the time and structural constraints of a clinical study. Similarly, the end-points and biomarkers selected may not reflect the full extent of its activity.

- **BCT-197** has impressive data in AECOPD, however, in our view, there is still a risk that Mereo BioPharma may not be able to find a partner. Over the past decade the p38 MAPK inhibitors have been one of the most heralded classes of therapies for treating inflammation. So far there has been limited success, albeit in chronic and not acute settings; for example, in Q316 AstraZeneca stopped development of its p38 programmes (AZD-7624) in COPD and related inflammatory respiratory conditions. However, Mereo BioPharma has indicated that it is confident that it will find a partner to fund further development of BCT-197 within 12 months.

- **BGS-649** has produced strong initial results from the Phase IIb study in HH and is now awaiting confirmatory results from the follow-on 6-month safety study, with results expected in Q418. The next stage will be to seek a commercialisation and/or development partner. The potential market for BGS-649 is large, given the level of obesity in many countries. However, it is a challenging market with established competitors, and any marketing campaign would need to educate primary-care physicians about testosterone deficiency and raise awareness among patients.

Further out, the sensitivities centre on the execution of the commercial strategy for programmes that will be marketed directly. Whilst this is an eminently sensible approach and addressing these well-defined therapy segments should not be unduly onerous, management has yet to prove itself at commercialising its assets.

Longer term, the reproducibility of the model needs to be demonstrated. To date only two deals, that have brought in four programmes, have been closed. The future deal flow will likely depend on the rate, and degree, of success achieved with these existing programmes. Inevitably, the better opportunities will be offered not simply to those with the bigger pockets but to those that have a proven track record of delivery.
Valuation

We believe an rNPV model to be the most appropriate way to value Mereo BioPharma. The rNPV of each individual clinical project is assessed and the success probabilities adjusted for the inherent clinical, commercial, and execution risks each carries. These are summed and netted against the costs of running the operation and net cash. The success probabilities are based on standard industry criteria for the respective stage of the clinical development process but, importantly, are flexed to reflect the inherent risks of the individual programme, the indication targeted, and the trial design. We have also factored an element for the execution and commercial risks, notably on the two programmes earmarked for partnering.

As always, we employ conservative assumptions throughout our modelling, particularly regarding market sizes and growth rates, net pricing, adoption curves, and peak market penetration. Our model results (see Exhibit 8) in a valuation of £510.3m, or 615.4p per share on a fully diluted basis, for Mereo BioPharma.

Exhibit 8: rNPV-based valuation of Mereo BioPharma

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<th>Total NPV ($)</th>
<th>Total NPV (£m)</th>
<th>Likelihood of approval</th>
<th>rNPV ($)</th>
<th>rNPV (£m)</th>
<th>rNPV/share (p)</th>
<th>Notes</th>
</tr>
</thead>
</table>
| BPS-804 (setrusumab) | 895.5         | 688.8          | 50%                    | 424.0    | 326.2     | 458.4          | Peak sales: $735m (£566m)
|                      |               |                |                        |          |           |                | Launch year: 2023       |
| MPH-966 (alvelestat) | 395.9         | 304.6          | 25%                    | 80.6     | 62.0      | 87.1           | Peak sales: $420m (£323m)
|                      |               |                |                        |          |           |                | Launch year: 2024       |
| *BCT-197 (acumapimod)| 269.9         | 207.6          | 60%                    | 115.9    | 89.2      | 125.4          | Peak sales: $768m (£591m)
|                      |               |                |                        |          |           |                | Launch year: 2023       |
| *BGS-649 (leflutrozole) | 134.1       | 103.2          | 50%                    | 29.4     | 22.6      | 31.7           | Peak sales: $483m (£372m)
|                      |               |                |                        |          |           |                | Launch year: 2024       |
| Operating costs     | (7.3)         | (5.6)          | (7.3)                  | (7.3)    | (5.6)     | (7.9)          |                        |
| Net cash            | 20.8          | 16.0           | 20.8                   | 16.0     | 16.0      | 22.5           | At June 2018             |
| Total               | 1,709.0       | 1,314.6        | 663.4                  | 510.3    | 717.3     | 615.4          | Based on all options, warrants, bonus shares and convertible debt |
| Total (fully diluted)|              |               |                        |          |           |                |                       |
| Discount rate       |               |                |                        |          |           |                | 12.5%                  |
| Exchange rate ($/£) |               |                |                        |          |           |                | 1.30                   |
| Taxation            |               |                |                        |          |           |                | 10.0% From 2026 with the benefit of UK Patent Box |

Source: Trinity Delta; Note: *The rNPV of BGS-649 and BCT-197 includes a deal success factor of 50% and 70% respectively. For the purpose of the valuation, the launch year is the first year of material sales.

BPS-804 valued at £326m, equivalent to 458p a share

Looking at the elements of our valuation in greater detail: BPS-804 is the largest component of the valuation, amounting to £326m, equivalent to 458p a share. We have assumed first material sales will occur in 2023, with peak sales of $735m (£566m) occurring some 6 years later with an operating margin of 60%. We have employed a 50.0% probability that it will successfully complete its clinical trials and reach the market. We view BPS-804 as being well suited to self-commercialisation by Mereo BioPharma, so have factored in appropriate costs for marketing, offset obviously by a greater retention of the revenues. Although the
precise terms of the payments to Novartis are not known\(^\text{10}\), we have assumed a 10% is paid away in the equivalent of royalties.

Our model shows MPH-966 to be worth £62m equivalent to 87p a share. We have based this on a first market launch in 2024, peak sales of $420m with an operating margin of 65% being achieved, and a clinical success probability of 25.0%. MPH-966 is also a product well suited to self-commercialisation, hence we have used similar financial assumptions to BPS-804, with a royalty equivalent rate of c 10% of revenues payable to AstraZeneca\(^\text{11}\). We have a higher gross margin assumption with MPH-966, compared to BPS-804, because it is a small molecule and not a monoclonal antibody.

Although BCT-197 has the largest sales potential, with peak sales of $768m following a first launch in 2023, and a clinical success probability of 60%, our valuation is £89m, equivalent to 125p a share. This again reflects the dynamics of out-licensing versus a self-commercialised product. We have used a success probability of a suitable deal taking place of 70% in 2019, with Novartis receiving 20% of any upfront or milestone payments and Mereo BioPharma achieving net royalties of 10% (after royalties payable to Novartis). We conservatively estimate that Mereo BioPharma will receive a $20m upfront, a $30m milestone payment on filing and $50m on approval.

BGS-649 is valued at £23m, equivalent to 32p a share. Here the first market launch occurs in 2024, peak sales are $483m, and the clinical success probability is 50%. To take into account the risks associated with partnering the asset, we conservatively assigned a success probability of 50% that this happens in 2020. We estimate that Mereo BioPharma will receive a $10m upfront, a $15m milestone payment on filing and $30m on approval, and thereafter net royalties of 10% (after royalty payments to Novartis).

We openly admit that we have employed conservative assumptions throughout our modelling. It is important to note that any number of incremental improvements on our base case scenarios could result in material uplifts in our valuation. Equally importantly, the visibility for the outlook of all four clinical programmes is increasing, with a rich news flow over the coming years. This suggests that there is significant upside potential, with multiple catalysts expected in the next 6 to 24 months. We intend to review the model regularly to reflect the progress that should be achieved.

\(\text{10\ Novartis is entitled to tiered royalty payments based on annual worldwide net sales at percentages ranging from the high single digits to low double digits. These are payable for ten years following the first commercial sale in each market. Novartis also receives an undisclosed, but small, percentage of the value of any out-licensing type of agreement. Antibody products (ie BPS-804) will pay low single-digit royalties on a country-by-country basis for the later of patent expiry or ten years from first launch in that country, with a maximum period of 12 years. Additionally, up to $3.25m is payable in development and regulatory milestones for each and any antibody product.}\)

\(\text{11\ The royalties payable to AstraZeneca are ascending based on tiered world-wide net sales and range from high single-digit to low double-digit. These last for the later of ten years or patent expiry in that particular country. Development, regulatory, and commercial milestones are payable up to a total of $115.5m in aggregate (which may be a combination of cash and/or shares). A small, unspecified, payment is due on any out-licensing deal.}\)
Financials

Over the last 18 months Mereo BioPharma has made material headway in progressing its clinical pipeline. Management is very transparent in the amount it spends on each programme, both in terms of R&D expenditure and the associated operating costs. From inception in March 2015 to December 2017 a total of around £92m has been spent, with a laudable £73m (some 86%) directly allocated to the development programmes.

Although the phasing of the spend varies to reflect the trials underway, the individual programme split is as follows: BPS-804 around £23m; MPH-966 some £500k (acquired in October 2017); BGS-649 circa £24m; and BCT-197 around £25m. Over the near-term the spend is expected to focus on the two self-commercialisation programmes (BPS-804 and MPH-966), as the programmes marked for out-licensing (BGS-649 and BCT-197) are expected to see the partner driving, and funding, the development process through to registration.

Looking ahead, we are expecting the investment in R&D to fall by 36% to £22.3m in FY18 as there are limited costs associated with BCT-197 this year and there were significant CMC (chemistry, manufacturing and controls) related expenses for BPS-804 in FY17 which are not repeated in FY18. In FY19, R&D expenses are forecast to grow by 10.4% to £24.6m due to the extra costs associated with the Phase III trial with BPS 804 and Phase II trial with MPH-966 more than offsetting the reduced investment in the other two programmes.

Administrative expenses are expected to increase by 27% to £8.9m in FY18. This is largely driven by the costs associated with the preparations for listing on NASDAQ. In FY19, these expenses are expected to fall by 27% to £6.5m, which reflects the core operating costs for the company.

As at June 2018 Mereo BioPharma held a cash position of £36.9m, with a further £8.2m received in August as the R&D tax credit relating to FY17. This should enable the company to operate to the end-of FY19.

The company extended its cash runway in FY17 by establishing a credit facility of £20m with Silicon Valley Bank and Kreos Capital, with a £10m tranche drawn down in August 2017 and a second £10m tranche in December 2017. Interest only payments were made until September 2018, with interest and capital then being repaid in 30 equal monthly instalments through to March 2021. The interest rate is fixed at an equivalent of 9.0% annually, with an additional amount equivalent to 7.5% of the principal (£1.5m) due on repayment. Warrants, exercisable through to August 2027, are attached to the loan; 363,156 are with the first loan tranche with an exercise price of £3.03, and 333,334 are with the second loan tranche with an exercise price of £3.30. The total of 696,490 warrants is equivalent to 0.98% of the existing issued share capital.

In October 2017 Mereo BioPharma took an option to acquire a selection of NE inhibitor assets, including MPH-966, from AstraZeneca. The upfront payment was $5m, made up of $3m in cash and 490,798 new Mereo BioPharma shares. If certain development, regulatory and commercial milestones are met, a total of up to $115.5m (in an undisclosed combination of cash and new Mereo BioPharma shares) could become due.
Mereo BioPharma has sufficient funds to execute its short-term plans, but it will clearly need extra capital to fund the pivotal Phase IIb/III study with BPS-804 in children with OI and take MPH-966 to market (including milestone payments to AstraZeneca). A reasonable cash cushion would also be helpful in enabling Mereo BioPharma to move quickly in funding additional development programmes, when it comes across interesting assets for acquisition or in-licensing. The company could raise significant funds from the out-licensing of BCT-197 and BGS-649 as well as from the issuance of equity.
### Exhibit 9: Summary of financials

#### Year-end: Dec 31 £'000s 2015 2016 2017 2018E 2019E

### INCOME STATEMENT

<table>
<thead>
<tr>
<th>Description</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018E</th>
<th>2019E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revenues</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cost of goods sold</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gross Profit</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>R&amp;D expenses</td>
<td>(5,445)</td>
<td>(24,563)</td>
<td>(34,607)</td>
<td>(22,270)</td>
<td>(24,586)</td>
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<td>G&amp;A expenses</td>
<td>(4,734)</td>
<td>(5,123)</td>
<td>(7,045)</td>
<td>(8,933)</td>
<td>(6,505)</td>
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<tr>
<td>Underlying operating profit</td>
<td>(10,179)</td>
<td>(29,685)</td>
<td>(41,652)</td>
<td>(31,203)</td>
<td>(31,092)</td>
</tr>
<tr>
<td>Share-based payments</td>
<td>(2,982)</td>
<td>(6,494)</td>
<td>(3,652)</td>
<td>(3,073)</td>
<td>(3,134)</td>
</tr>
<tr>
<td>EBITDA</td>
<td>(13,150)</td>
<td>(36,146)</td>
<td>(45,268)</td>
<td>(34,225)</td>
<td>(34,200)</td>
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<tr>
<td>Operating Profit</td>
<td>(13,161)</td>
<td>(36,179)</td>
<td>(45,304)</td>
<td>(34,276)</td>
<td>(34,226)</td>
</tr>
<tr>
<td>Financing costs/income</td>
<td>26</td>
<td>2,458</td>
<td>(1,647)</td>
<td>(1,042)</td>
<td>434</td>
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<tr>
<td>Profit Before Taxes</td>
<td>(13,136)</td>
<td>(33,722)</td>
<td>(46,951)</td>
<td>(35,318)</td>
<td>(33,792)</td>
</tr>
<tr>
<td>Adj. PBT</td>
<td>(10,153)</td>
<td>(27,228)</td>
<td>(43,299)</td>
<td>(32,245)</td>
<td>(30,657)</td>
</tr>
<tr>
<td>Current tax income</td>
<td>947</td>
<td>5,331</td>
<td>8,152</td>
<td>4,664</td>
<td>4,917</td>
</tr>
<tr>
<td>Net Income</td>
<td>(12,189)</td>
<td>(28,390)</td>
<td>(38,799)</td>
<td>(30,672)</td>
<td>(28,874)</td>
</tr>
<tr>
<td>EPS (p)</td>
<td>(101.5)</td>
<td>(63.4)</td>
<td>(56.2)</td>
<td>(43.1)</td>
<td>(40.6)</td>
</tr>
<tr>
<td>Adj. EPS</td>
<td>(78.5)</td>
<td>(51.0)</td>
<td>(51.9)</td>
<td>(39.4)</td>
<td>(36.8)</td>
</tr>
<tr>
<td>DPS (p)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>Average no. of shares (m)</td>
<td>12.0</td>
<td>44.8</td>
<td>69.0</td>
<td>71.1</td>
<td>71.1</td>
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<td>Gross margin</td>
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<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>EBITDA margin</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Underlying operating margin</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
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### BALANCE SHEET

<table>
<thead>
<tr>
<th>Description</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018E</th>
<th>2019E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current assets</td>
<td>13,845</td>
<td>60,778</td>
<td>63,177</td>
<td>34,565</td>
<td>9,024</td>
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<tr>
<td>Cash and cash equivalents</td>
<td>12,248</td>
<td>53,578</td>
<td>50,045</td>
<td>25,609</td>
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<tr>
<td>Short-term investments</td>
<td>0</td>
<td>2,500</td>
<td>2,500</td>
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<tr>
<td>Accounts receivable</td>
<td>396</td>
<td>767</td>
<td>509</td>
<td>585</td>
<td>585</td>
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<tr>
<td>Inventories</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other current assets</td>
<td>1,201</td>
<td>6,433</td>
<td>10,123</td>
<td>5,872</td>
<td>6,143</td>
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<tr>
<td>Non-current assets</td>
<td>26,017</td>
<td>25,987</td>
<td>33,159</td>
<td>32,816</td>
<td>32,814</td>
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<tr>
<td>Property, plant &amp; equipment</td>
<td>205</td>
<td>174</td>
<td>153</td>
<td>125</td>
<td>124</td>
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<tr>
<td>Intangible assets</td>
<td>25,813</td>
<td>25,813</td>
<td>33,005</td>
<td>32,690</td>
<td>32,690</td>
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<tr>
<td>Current liabilities</td>
<td>(3,978)</td>
<td>(3,209)</td>
<td>(9,618)</td>
<td>(11,441)</td>
<td>(11,639)</td>
</tr>
<tr>
<td>Short-term debt</td>
<td>0</td>
<td>0</td>
<td>1,940</td>
<td>5,644</td>
<td>(5,644)</td>
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<tr>
<td>Accounts payable</td>
<td>(3,978)</td>
<td>(1,121)</td>
<td>(3,024)</td>
<td>(2,281)</td>
<td>(2,478)</td>
</tr>
<tr>
<td>Other current liabilities</td>
<td>0</td>
<td>(2,088)</td>
<td>(4,654)</td>
<td>(3,516)</td>
<td>(3,516)</td>
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<tr>
<td>Non-current liabilities</td>
<td>(141)</td>
<td>(4,299)</td>
<td>(24,234)</td>
<td>(20,789)</td>
<td>(20,789)</td>
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<tr>
<td>Equity</td>
<td>35,743</td>
<td>79,257</td>
<td>62,483</td>
<td>35,151</td>
<td>9,411</td>
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</table>

### CASH FLOW STATEMENTS

<table>
<thead>
<tr>
<th>Description</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018E</th>
<th>2019E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operating cash flow</td>
<td>(6,673)</td>
<td>(29,287)</td>
<td>(31,423)</td>
<td>(24,605)</td>
<td>(25,788)</td>
</tr>
<tr>
<td>Profit before tax</td>
<td>(13,136)</td>
<td>(33,722)</td>
<td>(46,951)</td>
<td>(35,318)</td>
<td>(33,792)</td>
</tr>
<tr>
<td>Non-cash adjustments</td>
<td>3,109</td>
<td>5,100</td>
<td>6,451</td>
<td>3,835</td>
<td>2,726</td>
</tr>
<tr>
<td>Change in working capital</td>
<td>3,328</td>
<td>(1,988)</td>
<td>3,021</td>
<td>(845)</td>
<td>197</td>
</tr>
<tr>
<td>Interest paid</td>
<td>26</td>
<td>375</td>
<td>724</td>
<td>(430)</td>
<td>434</td>
</tr>
<tr>
<td>Taxes paid</td>
<td>0</td>
<td>947</td>
<td>5,331</td>
<td>8,152</td>
<td>4,646</td>
</tr>
<tr>
<td>Investing cash flow</td>
<td>(216)</td>
<td>(2)</td>
<td>(4,796)</td>
<td>(23)</td>
<td>(2,476)</td>
</tr>
<tr>
<td>CAPEX on tangible assets</td>
<td>(216)</td>
<td>(2)</td>
<td>(2,296)</td>
<td>(23)</td>
<td>(24)</td>
</tr>
<tr>
<td>Other investing cash flows</td>
<td>0</td>
<td>0</td>
<td>2,500</td>
<td>0</td>
<td>2,500</td>
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<tr>
<td>Financing cash flow</td>
<td>19,137</td>
<td>68,357</td>
<td>34,070</td>
<td>143</td>
<td>0</td>
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<tr>
<td>Proceeds from equity</td>
<td>20,005</td>
<td>67,889</td>
<td>15,000</td>
<td>150</td>
<td>0</td>
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<tr>
<td>Increase in loans</td>
<td>3,464</td>
<td>20,000</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other financing cash flow</td>
<td>(868)</td>
<td>(2,996)</td>
<td>(930)</td>
<td>(8)</td>
<td>0</td>
</tr>
<tr>
<td>Net increase in cash</td>
<td>12,248</td>
<td>39,067</td>
<td>(2,149)</td>
<td>(24,485)</td>
<td>(23,312)</td>
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<tr>
<td>Exchange rate effects</td>
<td>0</td>
<td>2,263</td>
<td>(1,384)</td>
<td>49</td>
<td>0</td>
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<tr>
<td>Cash at start of year</td>
<td>0</td>
<td>12,248</td>
<td>53,578</td>
<td>50,045</td>
<td>25,609</td>
</tr>
<tr>
<td>Cash at end of year</td>
<td>12,248</td>
<td>53,578</td>
<td>50,045</td>
<td>25,609</td>
<td>2,296</td>
</tr>
<tr>
<td>Net cash at end of year</td>
<td>12,248</td>
<td>50,451</td>
<td>31,792</td>
<td>7,204</td>
<td>(18,609)</td>
</tr>
</tbody>
</table>

Source: Mereo BioPharma, Trinity Delta; Note: Adjusted numbers exclude share-based payments and exceptionals.
Company information

Contact details

1 Cavendish Place, London, W1G 0QF, United Kingdom
Tel: +44 (0) 330 023 7300
www.mereobiopharma.com

Key personnel

<table>
<thead>
<tr>
<th>Person</th>
<th>Position</th>
<th>Biography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peter Fellner</td>
<td>Non-Executive Chairman</td>
<td>Joined as Chairman in July 2015. Also Chairman of Vernalis and Consort Medical. Previously Chairman and Director of several public companies including Ablynx, Optos, Astex Pharmaceuticals, Acambis, and Celltech.</td>
</tr>
<tr>
<td>Denise Scots-Knight</td>
<td>CEO</td>
<td>Co-founded Mereo BioPharma and CEO since July 2015. From 1999 to 2010 at Nomura Ventures as Managing Director, then leading a buy-out as Managing Partner of Phase4 Partners until 2015. Previously an Investment Manager at Rothschild Asset Management (1997-99). Other roles of rising seniority at Amersham, Fisons, and Scientific Generics. Holds a BSc(Hons) and PhD in Biochemistry from the University of Birmingham and Fulbright Scholarship to University of California, Berkeley (also Biochemistry).</td>
</tr>
<tr>
<td>Richard Jones</td>
<td>CFO</td>
<td>Joined as CFO in January 2017. Previously CFO at Shield Therapeutics from 2010, overseeing its successful IPO. Has held a number of senior investment banking positions (Brewin Dolphin, Investec) and advisory and consultancy roles (Grant Thornton, Bionow). Gained a BEng (Hons) from Newcastle University and is a qualified accountant (ACA with Price Waterhouse Cooper).</td>
</tr>
</tbody>
</table>

Top institutional shareholdings

<table>
<thead>
<tr>
<th>Institution</th>
<th>% holding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woodford Investment Management</td>
<td>42.0</td>
</tr>
<tr>
<td>Invesco Asset Management</td>
<td>26.9</td>
</tr>
<tr>
<td>Novartis Pharma AG</td>
<td>19.4</td>
</tr>
<tr>
<td>Canaccord Genuity Wealth Management</td>
<td>4.0</td>
</tr>
<tr>
<td>Directors and related holdings</td>
<td>4.0</td>
</tr>
<tr>
<td>Top institutional investors</td>
<td>96.3</td>
</tr>
<tr>
<td>Other shareholders</td>
<td>3.7</td>
</tr>
<tr>
<td>Total shareholders</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Source: Mereo BioPharma
Disclaimer

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