

Midatech Pharma

Pivoting its commercial strategy

Midatech is a drug-delivery technology company focused on re-engineering existing therapeutics to improve their bioavailability and delivery. A strategic review in 2020 has translated into a broadened pipeline with the Q-Sphera platform at its core (polymer microsphere technology for sustained drug release). The most clinically advanced asset is the Phase II ready MTX110 (MidaSolve platform, which liquifies insoluble oral therapies for improved drug delivery) targeting brain cancers such as diffuse intrinsic pontine glioma (DIPG) and glioblastoma (GBM). Prospective out-licensing deals for the Q-Sphera portfolio and start of the MTX110 Phase II trials in the coming months should be the next catalysts.

New strategy aimed at de-risking financial position

Following its 2020 strategic review, Midatech has pivoted its focus from end-to-end clinical development and commercialisation of a limited number of assets (MTD201 and MTX110) to a broader, early-stage asset portfolio (both in-house and partnered) with an aim to out-license before human trials (with the exception of legacy asset MTX110 for which the company will undertake clinical trials until a partner comes onboard). The objective is to minimise exposure to costly clinical trials and the front-end loaded nature of a commercialisation strategy albeit with some loss of upside and control.

Platforms scalable across therapeutic areas

The platform nature of Midatech's solutions offer the potential to develop multiple drug assets across a number of therapeutic areas, mitigating risks associated with a narrower portfolio focus. While 10 projects are currently under development across its platforms, Q-Sphera is the key focus with three in-house and partnered projects each, including long-acting injectable (LAI) versions of antipsychotic drug Brexpiprazole/MTD211, immunosuppressant Tacrolimus/MTD219 and potentially a monoclonal antibody (mAb). Peak sales potential runs upwards of a billion dollars.

Multiple near-term catalysts

With 'proof-of-concept' delivered for two partnered and one in-house asset, we expect the next few months to be eventful in terms of partnering possibilities. Phase II initiation for MTX110 (liquified panobinostat delivered through a convection enhanced delivery (CED) system for DIPG) in H122 should be another key catalyst.

Well-funded to progress development pipeline

The £10m equity raising in June 2021 alleviates funding pressure and could extend the cash runway into 2023, based on existing cash burn trends for the pipeline and assuming no licence fees/milestones.

Historical financials

| Year end | Revenue (£m) | PBT (£m) | EPS (p) | DPS (p) | P/E (x) | Yield (%) |
|----------|--------------|----------|---------|---------|---------|-----------|
| 12/17 | 7.60 | (15.8) | (568) | 0.0 | N/A | N/A |
| 12/18 | 1.94 | (11.8) | (339) | 0.0 | N/A | N/A |
| 12/19 | 0.67 | (10.9) | (50) | 0.0 | N/A | N/A |
| 12/20 | 0.34 | (11.1) | (23) | 0.0 | N/A | N/A |

Source: Midatech company filings. Note: PBT and EPS are normalised.

Pharma & biotech

17 September 2021

Price 25.5p
Market cap £26m

Share price graph



Share details

| | |
|---------------------------|-------|
| Code | MTPH |
| Listing | AIM |
| Shares in issue | 98.5m |
| Net cash at end June 2021 | £3.4m |

Business description

Midatech is platform-based drug delivery specialist founded in 2000 and listed on the AIM in 2014. Its three technology platforms, Q-Sphera (for sustained release of drugs), MidaSolve (nano inclusion for local delivery) and MidaCore (gold nanoparticles for targeted delivery) are designed to re-engineer and reformulate existing therapeutic drugs with the aim of improving biodistribution and delivery. The realigned focus is now on the Q-Sphera development pipeline and the clinical asset MTX110 (for brain cancer).

Bull

- Scalable technology platforms with a broad product pipeline.
- First-in-class potential in DIPG/brain cancers.
- Early success in encapsulating a mAb.

Bear

- Challenges in finding partners/out-licensing opportunities.
- Requirement for additional funding and potential equity dilution risk.
- Earlier-stage product out-licensing strategy may limit upside potential of partnership deals.

Analysts

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Investment summary

Company description: Facilitating drug-delivery

Midatech is a UK-based drug-delivery specialist, founded in 2000 and dual-listed on the AIM market of the London Stock Exchange and Nasdaq. The company specialises in improving the bio-delivery and biodistribution of existing medicines by leveraging its three technology platforms: Q-Sphera, MidaSolve and MidaCore. Following a strategic review in early 2020, Midatech has pivoted its focus from a narrow, targeted pipeline to a broader, albeit early-stage asset portfolio (both in-house and partnered) with an aim to partner following proof-of-concept (PoC). The goal is multi-fold: to diversify the pipeline risk, generate multiple partnering opportunities to monetise the company's technologies and alleviate the financing obligations on the company. The initial development focus will be on the Q-Sphera platform, which utilises proprietary 3D microsphere printing technology to develop sustained release formulations of existing therapeutics. Of the current pipeline (three in-house and three partnered compounds), PoC formulations have been delivered for two partnered (MTX214 and MTX216) and one in-house asset (MTD211, an LAI formulation of the antipsychotic drug Brexpiprazole), with partnering discussions expected to gain momentum in H221. The other in-house asset MTD219, an LAI version of the transplant anti-rejection drug Tacrolimus, has transitioned to the pre-clinical stage and Midatech expects to deliver the PoC formulation later this year. Another potentially exciting prospect, and one that holds blockbuster potential for Midatech, is an investigational LAI formulation of a mAb; the company released encouraging in-vitro data in June 2021. Success here could provide Midatech with an opportunity to target some of the most lucrative areas in drug development, such as oncology and autoimmune diseases. The other key programme comprises MTX110, the company's most clinically advanced asset (Phase II in H122), utilising proprietary nano-inclusion technology and a CED system to target aggressive brain cancers, with an initial focus on DIPG, followed by medulloblastoma and GBM.

Financials: Funded to early 2023

Midatech's much leaner organisational setup has allowed it to have a stronger control on its cash burn, with the company ending H121 with a net cash balance of £3.4m (cash of £4.2m less lease liabilities of £0.8m). The funding situation was bolstered further by a £10m UK placement in July 2021 (c 35.1m shares issued at 28.5p, a 12.3% discount to the pre-placement closing price of 32.5p). If the current operating expenditure run rate is sustained, we expect the additional fund inflow to extend Midatech's cash runway into 2023. We expect a need to raise a similar sum by early FY23, through partnerships and/or fund-raising.

Sensitivities: Execution risk is key

While Midatech is partially insulated from the typical biotech regulatory risks (the company applies its proprietary drug delivery technology to existing approved medicines), execution on its pipeline assets will be a key factor in determining the company's future outlook and direction. Midatech has had some setbacks in the past on this front, the most recent being the termination of its then lead Phase I programme, MTD201/Q-Octreotide, and closure of its Bilbao, Spain, manufacturing facility in [March 2020](#) due to financing related challenges. While the realigned focus on broadening the portfolio and employing a pure-play out-licensing strategy mitigates some of these risks, the ability to generate market interest in its platforms and get partners on board will be crucial to the company's development plans. Timely access to funding is another key sensitivity given the nascent pipeline and limited opportunity for internally generated capital in the near term. Despite a broad and promising pipeline, portfolio risk remains high given that the most advanced-stage asset MTX110 targets the high-risk brain cancer space (which has a very low success rate of approval).

and the Q-Sphera pipeline is at a very early stage of development. Successful progression of the pipeline and/or partnership wins could catalyse a robust re-rating of the stock.

Broader portfolio offers multiple shots at goal

Midatech is a development-stage company specialising in reformulating/re-engineering existing approved drugs to improve their delivery and biodistribution in major disease areas with high unmet medical needs. The current therapeutic focus is on the central nervous system, anti-organ-rejection and brain cancer. The group's three in-house technology platforms – Q-Sphera, MidaSolve and MidaCore – are designed to facilitate targeted delivery and sustained release of therapeutics:

- Q-Sphera: polymer microsphere technology used for sustained release to prolong and control the release of therapeutics over an extended period of time (from weeks to months);
- MidaSolve: nanosaccharide technology used to dissolve drugs so that they can be administered in liquid form directly and locally into tumours; and
- MidaCore: gold nanoparticle technology used for targeting medications to sites of disease.

Following a strategic review in March 2020, the company has now streamlined its strategy, moving away from its traditional focus on developing and commercialising advanced-stage assets (and the need for sizeable initial investment and associated risk) to a broader, early-stage portfolio (both in-house and in collaboration with third-party pharma companies) of long-acting formulations of approved therapeutics. The aim is to out-license or partner immediately after achieving PoC, which in Midatech's case translates to achievement of the desired profile for the formulation in terms of drug loading, injectability and dissolution for improved targeting and delivery (since the active pharmaceutical ingredient's (API's) approved indication(s) do not change). With 10 programmes currently under development (versus two prior to the strategic review: MTX110/Panobinostat and the now terminated MTD201/Q-Octreotide), the revamped pipeline looks to be more robust and underscores the company's business strategy to diversify its pipeline risk, generate potential income streams and manage funding requirements. While for legacy asset MTX110 the company will be initiating Phase II studies in H122, MTD201 remains open to out-licensing, although further in-house development has been terminated.

The near-term focus for Midatech, as indicated by management, will be on its Q-Sphera platform, which has been gaining traction, with the company bagging a scalable three-product collaboration deal with the European affiliate of an undisclosed global healthcare company in July 2020. In addition to these partnered programmes (of which PoC formulations have been delivered for two assets, MTX214 and MTX216; partner to undertake in vivo studies), Midatech is also developing three in-house assets: MTD211 (LAI version of antipsychotic drug Brexpiprazole, currently being marketed by Otsuka/Lundbeck under the brand name Rexulti), MTD219 (LAI version of the off-patent anti-rejection drug Tacrolimus marketed by Astellas under the brand name Prograf) and an LAI version of a mAb (targeted indication or area is currently undisclosed). The first two are currently in the pre-clinical stage while the third asset is investigational. We estimate both MTD211 and MTD219 to have peak sales potential of \$250–500m, which could translate into an attractive income stream following out-licensing. The long-acting formulation of a mAb presents an even bigger (potentially blockbuster) opportunity, should it progress, given there are currently no approved LAI mAbs in the market. Early indications are encouraging with the company announcing its success in encapsulating an exemplar mAb in [June 2021](#) while preserving its functional integrity and antigen binding in vitro.

Other than the Q-Sphera portfolio, Midatech's only clinical asset, MTX110 (liquified chemotherapy drug panobinostat delivered through a CED system), part of the MidaSolve platform, is being developed initially for the treatment of the ultra-rare and aggressive childhood brain tumour DIPG (c 1,000 newly diagnosed cases worldwide annually with a median survival of 10 months) and is

expected to begin enrolment for Phase II trials in H122 with a target completion of 2023/4. A pilot GBM study will commence at the same time with an estimated read-out in 2022/3. While the recent £10m fund-raising means that the clinical progression plan remains on track, the termination of the panobinostat licence by owner Secura Bio in June 2020 could add delays to MTX110's eventual commercialisation.¹ Midatech still holds the right to use panobinostat for research purposes (ie, in clinical trials), but in the absence of a mutual agreement with Secura Bio, the company will have to wait for the panobinostat patent expiry in 2026 before commercialising the asset. The best-case scenario otherwise would have been 2024/5, provided the company received approval from the US FDA). The current development pipeline is summarised in Exhibit 1.

Exhibit 1: Midatech's current development pipeline

| Programme | Active pharmaceutical ingredient | Therapeutic area | Administration | Development phase | Partnering status | Notes |
|------------------|----------------------------------|--|--------------------------|-------------------|-------------------|---|
| MidaSolve | | | | | | |
| MTX110 | Panobinostat | DIPG | Direct to tumour via CED | Phase II (H122) | In-house | Direct-to-tumour delivery of solubilised Panobinostat (using nano inclusion technology) delivered through a CED system. One Phase I study (seven participants) reported material improvement in survival data (26 months vs 10 months). Phase II study (21 participants) using a different CED system is expected to commence in H122 with read-out in 2023/4. Secura Bio's termination of the panobinostat licence may push market entry to beyond 2026 (following patent expiration of panobinostat). Midatech is currently in out-licensing talks with a potential co-development partner. Market potential c \$100m |
| MTX110 | Panobinostat | Medulloblastoma | Direct to tumour | Phase I | In-house | Same formulation as for DIPG but delivered through a different infusion device into the fourth ventricle. Targeting recurrent medulloblastoma (c 20% of cases), estimated to be similar market opportunity as DIPG. Phase I study ongoing with the University of Texas Health Science Center |
| MTX110 | Panobinostat | Glioblastoma | Direct to tumour via CED | Phase I (H122) | In-house | Phase I trials for MTX110 in GBM to be held concurrent to the DIPG phase II trials by Columbia University. Potentially a \$2–5bn market opportunity, according to management |
| Q-Sphera | | | | | | |
| MTD211 | Brexipiprazole | Schizophrenia, major depressive disorder | Long acting injectable | Pre-clinical | In-house | Developing an LAI version of Otsuka/Lundbeck's Brexpiprazole, an antipsychotic. We project a peak sales potential of >\$500m for MTD211 if successfully commercialised. PoC delivered with formulation optimisation ongoing |
| MTD219 | Tacrolimus | Immunosuppression in organ transplant recipients | Long acting injectable | Pre-clinical | In-house | Developing an LAI version of immunosuppressive drug Tacrolimus. Extended-release versions currently available in once-a-day tablets and capsules (Envarsus XR and Astagraf XL). We project a peak sales potential of \$250–400m for MTD219 if successfully commercialised |
| MTD220 | Monoclonal antibody | Undisclosed | Long acting injectable | Formulation | In-house | Investigational. Showcased success in encapsulating an exemplar mAb in in-vitro studies without denaturing it (June 2021) |
| MTX213 | Undisclosed | Undisclosed | Undisclosed | Formulation | Partnered | Partnered programme with the European affiliate of an undisclosed global healthcare company. Details unavailable |
| MTX214 | Undisclosed | Undisclosed | Undisclosed | Formulation | Partnered | Partnered programme with the European affiliate of an undisclosed global healthcare company. PoC achieved and formulation delivered to partner in June 2021. Partner to undertake in-vivo studies |
| MTX216 | Undisclosed | Undisclosed | Undisclosed | Formulation | Partnered | Partnered programme with the European affiliate of an undisclosed global healthcare company. PoC achieved and formulation delivered to partner in June 2021. Partner to undertake in-vivo studies |
| MidaCore | | | | | | |
| MTX114 | Methotrexate | Psoriasis, atopic dermatitis | Topical | Pre-clinical | In-house | Formulation of methotrexate using the MidaCore gold nanoparticle technology for targeted delivery of the therapeutic for mild to moderate psoriasis (reduces systemic toxicity related to methotrexate) |

Source: Midatech, Edison Investment Research

¹ Midatech in-licensed rights to use panobinostat for application in brain tumours using a CED system from original developer Novartis in June 2017, but the global licence was subsequently acquired by Secura Bio in March 2019.

Q-Sphera: Sustained release technology

Q-Sphera is Midatech's patented sustained-release drug delivery platform, developing extended-release injectable versions of active drug compounds using the company's patented 3D printing technology to encapsulate drugs into bioresorbable polymer microspheres (Exhibit 2). The microsphere platform uses the company's patented piezoelectric 3D printing technology to create precise formation of polymer beads between 30–70µm in size (microspheres are produced at a rate of 120,000 per second from each injector head). The microspheres, once injected, form depots in the body, which release the drug over predetermined, sustained periods from one week to six months. The drug release rates of the encapsulated therapeutics can be varied by changing the ratio of lactic acid to glycolic acid in the poly lactic-co-glycolic acid (PLGA) coating. Moreover, the physical characteristics, such as surface porosity and internal morphology, can be tailored to deliver a wide range of therapeutics, from small molecules to peptides and potentially biologics. Midatech currently has three non-GMP production lines for R&D purposes that can be scaled up as required. For clinical development, the company plans to seek support from a GMP certified contract development and manufacturing organisation (CDMO). Midatech maintains that the platform is scalable with a low-cost footprint and new formulations could be added quickly, if required. Each of the printing heads can be parallelised to increase productivity and the company's scale-up blueprint is targeting up to 20 injector heads per unit.

Exhibit 2: The Q-Sphera technology platform



Source: Midatech

Q-Sphera's positioning in the PLGA microsphere space

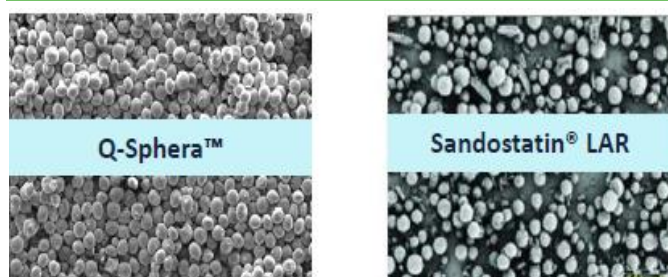
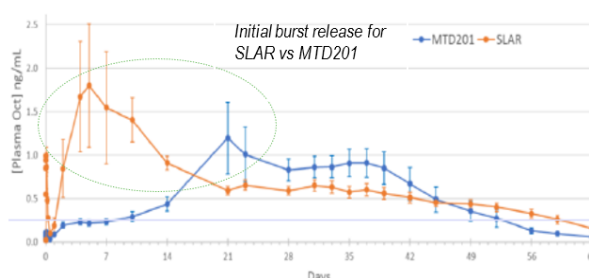
Although there are clear advantages of having long-acting depot formulations of available therapeutics (especially in disease areas where dosing conformity is critical or where patient compliance is suspect), PLGA microsphere-based therapeutics have been slow to transition from the clinic to the market, with fewer than 15 drugs approved in the category in the past three decades (since approval of Takeda/AbbVie's once-monthly prostate cancer injectable Lupron in 1989) (Exhibit 3). This highlights the likely challenge in developing such therapeutics.

Exhibit 3: FDA-approved PLGA microsphere-based sustained release formulations

| Product name | Company | API | Indication | Route of administration | Duration | Approval |
|------------------|----------------------|--------------------------|--|-----------------------------|----------------|------------------------|
| Lupron | Takeda/AbbVie | Leuprolide acetate | Prostate cancer, endometriosis, central precocious puberty | Intramuscular | 1,3,4,6 months | 1989, 1996, 1997, 2011 |
| Sandostatin LAR | Novartis | Octreotide acetate | Acromegaly | Subcutaneous | 1 month | 1998 |
| Trelstar | Allergan | Triptorelin pamoate | Prostate cancer | Intramuscular | 1,3,6 months | 2000, 2001, 2010 |
| Arestin | Bausch Health U.S. | Minocycline HCl | Periodontitis | Periodontal | 2 weeks | 2001 |
| Risperdal Consta | Janssen | Risperidone | Schizophrenia, bipolar disorder | Intramuscular | 2 weeks | 2003 |
| Vivitrol | Alkermes | Naltrexone | Opioid antagonist | Intramuscular | 1 month | 2006 |
| Bydureon | AstraZeneca | Exenatide | Type 2 diabetes | Subcutaneous | 1 week | 2012 |
| Signifor LAR | Novartis | Pasireotide pamoate | Acromegaly | Intramuscular | 1 month | 2014 |
| Zilretta | Flexion Therapeutics | Triamcinolone acetoamide | Knee osteoarthritis | Intra-articular | 3 months | 2017 |
| Bydureon BCise | AstraZeneca | Exenatide | Type 2 diabetes | Subcutaneous | 1 week | 2017 |
| Triptodur Kit | Arbor | Triptorelin pamoate | Central precocious puberty | Microsphere, intraarticular | 6 months | 2017 |

Source: Jana Ghitman et al., Review of hybrid PLGA nanoparticles: Future of smart drug delivery and theranostics medicine, *Materials & Design*, Volume 193, 2020, Edison Investment Research

Some of the key obstacles hindering more widespread use of PLGA microsphere technology include low drug loading, high initial burst release (as much as 100 times the steady-state drug concentration in some cases) and/or poor formulation stability. The Q-Sphera technology platform claims to address/mitigate these issues and proposes the results for the Phase I exploratory trial for MTD201 (internal development subsequently terminated on funding constraints) as a validation of its technologic advantages against competing therapeutics. The company asserts that using the piezo-electronics 3D printing technology enables it to maintain control of particle size, drug loading, injectability and dissolution, ensuring predictable pharmacokinetics with low variability in blood drug concentrations. The homogeneous particle size also allows for a tighter microsphere distribution, increasing the therapeutic yield. The company was able to highlight these properties in its results from the [MTD201 Phase I exploratory study](#) where the drug showcased a superior clinical profile in a head-to-head comparison with standard of care Novartis's Sandostatin LAR (SLAR): no measurable burst release or dose-dumping and the ability to use a smaller 21-gauge needle (versus a 19-gauge for SLAR) for administration of the drug (Exhibits 4 and 5).

Exhibit 4: MTD201 microsphere distribution versus SLAR

Exhibit 5: MTD201 pharmacokinetics versus SLAR


Source: Midatech corporate presentation, January 2021

Source: Midatech corporate presentation, January 2021; with Edison annotations

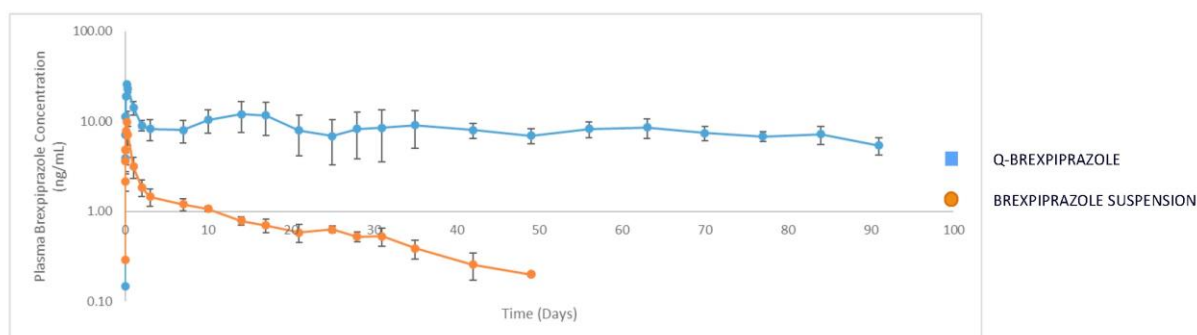
MTD211/Q-Brexipiprazole

MTD211, the LAI formulation of second-generation antipsychotic Brexpiprazole, is the most advanced Q-Sphera programme currently under development. The drug, developed by Otsuka and marketed under the brand name Rexulti, is currently approved as monotherapy for schizophrenia and as an adjunct for major depressive disorder (MDD). Label expansion studies are ongoing by Otsuka in agitation in Alzheimer's disease (Phase III), borderline personality disorder (Phase III) and post-traumatic stress disorder (Phase II). Currently the drug is only approved as an oral tablet and Midatech reports to be on track to develop a three-month depot injection, suitable for

subcutaneous application (which should be less painful compared to the intramuscular administration of other approved LAI antipsychotics) with a possibility to be used with self-injecting devices (ensuring ease of use, fewer office visits and lowering of healthcare system costs).

Recent in-vivo studies conducted by Midatech, which pitched MTD211 head-to-head against a suspension brexpiprazole formulation (representative of the technology used in competing sustained release antipsychotic products), reported encouraging data. MTD211 was able to achieve a drug loading of 20% (meaning that 20% of the microsphere mass consists of the drug), enabling a therapeutically relevant dose to be consistently delivered over 90 days according to the company, with minimal burst release, showcasing discernible improvement over the comparator suspension formulation (see Exhibit 6).

Exhibit 6: Plasma brexpiprazole concentrations in rabbits after a single SC Depot Injection (n=4)



Source: Midatech corporate presentation, June 2021

The next steps for MTD211, according to the company, would be to further optimise the formulation based on modelling of human pharmacokinetic steady state simulations. Alongside this, Midatech would also begin engaging with potential licensing partners and working towards GMP manufacturing to support clinical development.

The antipsychotic market landscape

MTD211 is targeting the sizeable antipsychotic market, estimated to be worth c \$16.5bn in 2020 and forecast to grow to c \$21.8bn by 2027, at a CAGR of 4.1%. Schizophrenia, the likely first indication for MTD211, afflicts 1.1% of the US adult population, translating into 2.8 million people suffering from this mental disorder in the US alone (c 3.8 million in the EU and UK). According to Evaluate Pharma, the therapeutic market for schizophrenia was worth \$10.2bn in 2020 and is estimated to reach \$13.6bn by 2026 (a CAGR of 4.9%). A key issue with this market is the high non-adherence rate in schizophrenia patients, ranging from 40–80% of patients. As a result, there has been an increasing trend towards adoption of LAI antipsychotic drugs, which come with the benefit of potentially improved compliance, fewer hospitalisations and therefore lower payor costs. LAI penetration currently stands at 50–55%, but significant potential remains both in terms of market share and market scope. This creates a meaningful opportunity for MTD211 given that there are currently no approved LAI versions of Brexpiprazole in the market; the drug recorded c \$1bn (JPY104.6bn) in sales in 2020.² However, making inroads into the space could be challenging given multiple LAIs of other antipsychotic drugs are firmly entrenched in the market, led by market leader Janssen (Johnson & Johnson) with its one-month and three-month versions of API paliperidone palmitate, Invega Sustenna and Invega Trinza, together registering c \$3bn in sales in 2020. Other key LAI versions in the market includes Otsuka's Abilify Maintena (aripiprazole), Alkermes' Aristada (aripiprazole lauroxil) and Janssen's Risperdal Consta (risperidone). On 1 September 2021, Janssen also received approval from the US FDA for its longer bi-annual version of paliperidone palmitate, called Invega Hafyera. It is the first twice-yearly treatment to be approved and is likely to

² Otsuka Pharmaceuticals annual report 2020

intensify the competition in the LAI antipsychotic space. Nonetheless, given the large market size, we expect even a modest 5% market share of the schizophrenia drug market to offer peak sales of over \$500m for MTD211. Label expansion opportunities could add further upside.

MTD219/Q-Tacrolimus

The other in-house asset, MTD219, is an LAI version of off-patent immunosuppressant drug tacrolimus, generally prescribed as an anti-rejection oral medication to transplant recipients. There are broadly four classes of maintenance immunosuppressants prescribed to transplant patients:

- calcineurin inhibitors: Tacrolimus and Cyclosporine;
- antiproliferative agents: Mycophenolate Mofetil, Mycophenolate Sodium and Azathioprine;
- mTOR inhibitors: Sirolimus and Everolimus; and
- steroids: Prednisone.

The calcineurin-inhibitor class has been dominating the immunosuppression market, with tacrolimus being the preferred drug due to its potency and manageable side-effect profile. According to Grand View Research, the global organ transplant immunosuppressant drugs market was valued at \$4.64bn in 2018 and is expected to reach \$5.82bn by 2026, registering a CAGR of 3.3% during the forecast period. Kidney transplants hold the largest market share, accounting for c 60% of all transplants. According to the U.S. Department of Health & Human Services, 22,817 kidney transplants took place in the US in 2020 out of a total 39,306 transplants (including heart, liver, lungs, pancreas). The corresponding EU figure stood at 21,235 in 2019 (34,285 total).³ Tacrolimus is prescribed in c 85% of all kidney transplant cases.

The tacrolimus active ingredient, which was developed by Astellas Pharma and is sold under the brand name Prograf, has been off patent since 2008, with several generic versions available in the market. Despite this, Prograf recorded sales of c \$1.7bn in 2020 and continues to be the clear market leader. While potent, tacrolimus is currently administered as oral pills required to be taken twice a day, resulting in inter- and intra-patient variability, possible dose-related toxicity and sub-optimal patient compliance, each of which individually could lead to graft failure. This highlights the untapped need for a longer-acting alternative. While a couple of extended releases versions are currently available in the market, none of them provide a substantially longer dosage interval versus the current standard of care. Both approved extended-release versions offer once-a-day dosage (Astagraf XL from Astellas Pharma and Envarsus XR from Veloxis Pharmaceuticals/Asahi Kasei), only a slight benefit over the underlying original drug. Envarsus XR is believed to have a superior pharmacokinetic profile over Astagraf XL with Asahi Kasei expecting peak sales in the range of \$700–800m in the US by 2028 (sales stood at \$122m in FY20). Asahi Kasei acquired Envarsus XR's developer Veloxis Pharmaceuticals in 2019 for \$1.3bn (EV/sales multiple of c 15x), underscoring the positive market sentiment around extended-release versions of the therapeutic.

Midatech's LAI version (which has progressed from formulation to the pre-clinical stage) could offer an added advantage of a significantly longer dosage interval (although the targeted dosage interval has not been communicated by the company). Moreover, given that tacrolimus has a narrow therapeutic index (too high a dose may lead to immune over-suppression/risk of infection, too low a dose increases risk of transplant rejection), the company's LAI formulation (which promises consistent plasma concentration within the therapeutic window) could potentially offer significant advantages. According to our research, there are currently no LAI versions of tacrolimus undergoing clinical trials, although competitor MedinCell has recently initiated pre-clinical studies for its LAI tacrolimus formulation. While we currently do not have information on the dosage frequency of MTD219, a sufficiently longer dosage interval to currently approved oral LAIs could potentially allow the drug to record sales numbers in the range of \$250–400m, following clinical validation, in our view. The company expects to deliver PoC on MTD219 in H221, followed by out-licensing discussions with potential partners.

3 Council of Europe, international figures on donation and transplantation 2019

MTD220/LAI mAb: High risk-reward trade-off

A key constituent to Midatech's Q-Sphera pipeline and one that has been a major talking point in recent months is its investigational programme to develop a sustained release version of large molecule biologics (>150kDa in size), in particular mAbs. Monoclonal antibodies are one of the most important classes of therapeutic and have revolutionised treatment modalities and outcomes in a number of critical disease areas such as oncology and autoimmune diseases. The mAb class also offers the scope to develop novel formulations for improved patient compliance, lifecycle management and reduced payor costs. However, efforts at developing an LAI formulation for large molecule drugs have been hampered by the delicate nature and pharmacokinetic properties of these molecules, which make them sensitive to the environment and not stable enough to withstand the heat, solvent interface and sheer forces associated with traditional PLGA microsphere-based manufacturing processes (such as double emulsion), resulting in denaturation of the protein. Developing stable, long-acting protein formulations capable of delivering a therapeutic dose over a prolonged period has proven difficult in the past as evidenced by the lack of any approved sustained release mAbs to date.

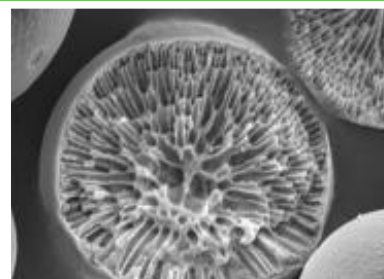
Midatech claims that its proprietary manufacturing process is relatively benign and gentle on these large molecules. According to the company, Q-Sphera's signature 'open honeycomb' structure creates microspheres without inaccessible points (that could result in pockets of protein degradation), see Exhibit 8. The company also maintains that its success with formulating short-chain peptides (MTD201/Q-octreotide) can be extrapolated to large molecules.

Exhibit 7: Exemplar structure of an immunoglobulin G mAb



Source: Midatech corporate presentation, June 2021

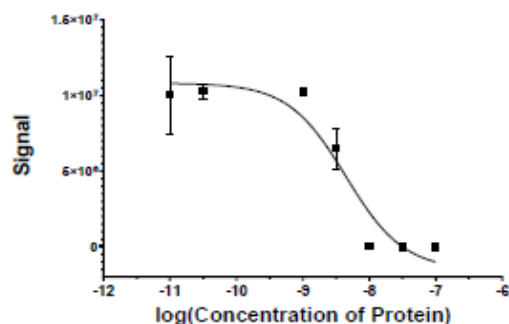
Exhibit 8: Q-Sphera microsphere structure



Source: Midatech corporate presentation, June 2021

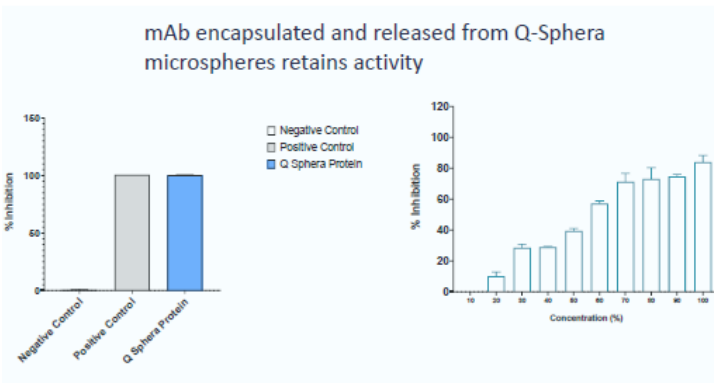
In June 2021, Midatech announced the results from an in-vitro assay study aimed at encapsulating an exemplar mAb, without losing functionality or denaturing the molecule. The assay measured the ability of the exemplar therapeutic monoclonal antibody to specifically combine with a carbonate antigen in order to demonstrate its binding and functional capabilities. It also assessed the activity of a Q-Sphera encapsulated mAb, released in an in-vitro dissolution model (representative of microsphere drug release in human bodies) against a heat inactivated negative control and a high-dose immediate release positive control (Exhibits 9 and 10).

Exhibit 9: Assay sensitivity to increasing concentration of the exemplar mAb



Source: Midatech corporate presentation, June 2021

Exhibit 10: Q-sphera encapsulated mAb activity versus controls



Source: Midatech corporate presentation, June 2021

The results for the in-vitro study indicated that the Q-Sphera encapsulated mAb retained and demonstrated full activity, similar to the high-concentration immediate-release positive control. The study also showed a linear relationship between protein concentration and assay inhibition (ie increased antibody binding). While academic publications have shown similar results in the past, these have been on a much smaller scale and, according to Midatech, the associated API wastage makes them uneconomic to develop at a commercial scale. The next focus for the company would be to further optimise the drug loading and dissolution profile and replicate the data from the first exemplar mAb, before evaluating potential application across different mAb therapeutics.

Market potential

Given that there are currently no long-acting mAbs on the market, Midatech's long-acting formulation (if successfully progressed) could offer sizeable potential, underpinned by its promise of improved protein stability, enabling a longer dosage interval and possibly an easier administration (subcutaneous vs the currently used intramuscular injection or intravenous infusion). The company has also cited the optionality for local mAb delivery (vs the systemic delivery currently applied) wherein regional administration to a targeted disease site for certain indications could reduce drug related toxicities as well as required dosage, together contributing to reduced healthcare costs.

The global sales revenue from mAb drugs was estimated to be \$163bn in 2019, making up for c 70% of sales of all biopharmaceutical products (c \$230bn).⁴ The top 10 mAbs alone contributed \$74.9bn to this figure in 2020, led by Humira, which has been the best-selling drug globally for many years (\$19.8bn in 2020, Exhibit 11). With 125 approved mAb products currently on the market and multiple therapeutics under development across a range of indications, the market potential for an LAI mAb Midatech product remains strong, with multiple avenues for income generation. In addition to developing in-house mAb programmes, the company could potentially also offer lifecycle management opportunities or additional IP to currently marketed drugs nearing their patent cliffs.

⁴ <https://bioprocessintl.com/business/economics/the-market-for-therapeutic-mab-products/>

Exhibit 11: Top 10 monoclonal antibodies by sales

| Drug | Generic name | Company | Administration | 2020 sales (\$m) | US patent expiry |
|----------|---------------|----------------------|--|------------------|------------------|
| Humira | Adalimumab | AbbVie | Injection every 2 weeks | 19.8 | 2023/2034 |
| Keytruda | Pembrolizumab | Merck | Injection every 3 weeks | 14.4 | 2028 |
| Stelara | Ustekinumab | Johnson & Johnson | Injection at 0 and 4 weeks then every 12 weeks | 7.7 | 2023 |
| Opdivo | Nivolumab | Bristol Myers Squibb | Injection every 4 weeks | 7.0 | 2028 |
| Avastin | Bevacizumab | Roche | Injection every 2 or 3 weeks | 5.0 | 2019 |
| Ocrevus | Ocrelizumab | Roche | Injection 2 weeks, every 6 months | 4.4 | 2023 |
| Rituxan | Rituximab | Roche | Infusion, 4 or 24 weeks | 4.3 | 2018 |
| Darzalex | Daratumumab | Johnson & Johnson | Injection weekly, then 3 weekly, then 4 weekly | 4.2 | 2034 |
| Soliris | Eculizumab | Alexion | Infusion, weekly then every two weeks | 4.1 | 2019/2027 |
| Cosentyx | Secukinumab | Novartis | Injection every 4 weeks | 4.0 | 2032/2036 |

Source: Midatech investor presentation, June 2021, Edison Investment Research

While there are other technologies being developed in the biotech space to improve the stability of large molecules (including using artificial intelligence and machine learning), Midatech maintains that its Q-Sphera technology offers the benefit of stability with enhanced bioavailability and biodistribution, which can be scaled up to commercial levels while ensuring consistency and robustness. The company plans to release further data on the development of its long-acting mAb programme in the coming months. As with the other Q-Sphera pipeline assets, the plan is to out license following PoC. If successfully commercialised, this would offer a blockbuster opportunity for Midatech, in our view, although at this stage risk remain fairly high. Positive development on this front could materially catalyse the company's market valuation, in our opinion.

MTX214 and MTX216: Partnered programmes

In addition to its in-house programmes, Midatech has also been developing three partnered assets as part of its July 2020 agreement with the European affiliate of an undisclosed global healthcare company. The brief was to apply the company's Q-Sphera technology platform to develop sustained release versions of APIs nominated by the partner, with all development costs to be reimbursed the partner at a multiple of the expenses. In an encouraging development, Midatech announced that it has been able to deliver PoC for two of the three programmes under development, MTX214 and MTX216. While the details of the two assets are currently unavailable, the company has indicated that the partner is in the process of conducting in-vivo studies, with the results expected in Q421. If successful, Midatech expects the companies to proceed with a licence agreement to offer access to Q-Sphera's IP. Further progression and clarity on this front should create an upside opportunity for the company.

MidaSolve: Nano inclusion technology platform

Midatech's MidaSolve platform is based on the company nano inclusion (NI) technology, which increases the aqueous solubility of drugs, using complexes that solubilise these agents in water, thereby enabling them to be injected in liquid form directly into tumours. This technique is suitable for small molecule chemotherapy drugs as they have strong potency but are poorly soluble and can thus only be administered orally in solid form. More importantly, this allows for high drug concentrations to be delivered directly to the tumour while simultaneously minimising systemic toxicity and other side effects. While solubility can also be achieved through organic solvents such as ethanol or dimethyl sulfoxide (DMSO), these may be harmful to the human body and are not recommended for the treatment of brain cancers such as glioma.

The MidaSolve platform uses its NI technology to encapsulate the chemotherapeutic in a complex composed of a hydrophilic outer surface and a hydrophobic inner surface. The poorly water-soluble drugs can then bond to the inner surface of the complex while the hydrophilic outer surface can associate, and solvate, with surrounding water molecules in the liquid form.

MTX110: Targeting lethal brain cancers

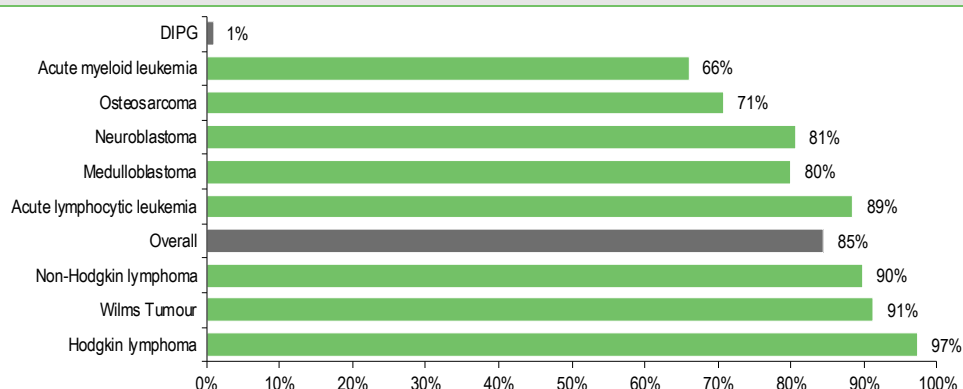
MTX110, Midatech's first product from its MidaSolve platform, is a soluble formulation of the potent chemotherapeutic panobinostat, delivered through a CED system for the treatment of brain cancers. The initial indication being targeted is childhood brain tumour DIPG, a highly aggressive and inoperable form of brain cancer. Midatech has undertaken two separate Phase I trials; one of the trials released headline data in October 2020, reporting encouraging overall patient survival (26 months vs 10 months with current standard of care; more details in subsequent sections). Midatech plans to start enrolment for Phase II clinical trials in H122 in the United States (expected endpoint of overall patient survival after 12 months) with headline data expected in 2023/4. The Phase II study will be an open-label study in a cohort of 21 newly diagnosed patients between three and 18 years of age. MTX110 will be administered via an alternate pump and catheter CED system (six cycles of 48-hour continuous infusion, two to four weeks apart). The primary objective of the study will be to assess the safety and tolerability of the administered dose as well as overall survival at 12 months (OS12). The secondary endpoints will be median overall survival (OS), progression-free survival (PFS) and PFS at six months.

In addition to DIPG, the company is also planning to initiate a pilot, signal finding study in GBM in H122 and is evaluating the utility of MTX110 in recurrent medulloblastoma in a [pilot Phase I study at the University of Texas](#). MTX110 received an orphan drug designation by the FDA in October 2019, which could allow it to file for accelerated approval following the Phase II studies provided sufficiently positive data is observed and could also accord it seven years of market exclusivity.

DIPG: A challenging landscape

DIPG is a highly aggressive childhood brain tumour originating in the back of the brain, in an area of the brainstem known as the pons. DIPG primarily affects children, with most cases occurring between five and seven years of age. Despite representing only 10–15% of all brain tumours in children (translating into 150–300 newly diagnosed cases per year in the United States,⁵ c 1,000 globally), it is the most prevalent cause of death due to brain cancer in children. The prognosis remains poor with an average survival of nine to 10 months, following standard treatment. The overall survival stands at 30% at one year, which goes down to 10% at two years, with <1% making it to the five-year mark. This is, by far, the worst prognosis for any childhood cancer (see Exhibit 12).

Exhibit 12: Selected paediatric cancers' five-year survival rates



Source: SEER Cancer Statistics Review, 1975–2017, National Cancer Institute

Despite years of research and clinical development, the treatment modality remains restricted with no approved drugs. Surgical resection is not possible due to the location of the tumour and no systemic chemotherapy drugs have been found to have an impact on survival yet (although

5 <https://dipg.org/dipg-facts/what-is-dipg/>

whether the lack of response is due to tumour resistance or dose insufficiency of systemic therapeutics is unclear). Radiation therapy is the standard of care (shrinking the tumour in c 80% of cases), although the tumour tends to recur in a few months. Therapeutic challenges for DIPG arise from the location of the tumour (pons is responsible for vital bodily functions such as heartbeat, breathing, sleeping, bladder control and balance, and therefore tumours in the area cannot be surgically resected) and difficulty in drug delivery across the blood-brain barrier (BBB) making both chemotherapeutics and targeted therapies ineffective.

To date, [over 250 clinical trials have been undertaken for DIPG](#), including standard chemotherapeutic agents administered in different intensities and timings, biologic and targeted agents, immunotherapy along with radiation therapy, but none have been effective in significantly improving the event-free survival (EFS) or OS of patients despite pre-clinical promise (see Exhibit 13).

Exhibit 13: Headline data from selected clinical trials in the treatment of DIPG

| Therapy/target | Year of reported headline data | Study phase | Number of evaluated patients | Median PFS (months) | Median survival (months) | OS at one year (%) |
|---|--------------------------------|-------------|------------------------------|---------------------|--------------------------|--------------------|
| Chemotherapeutics | | | | | | |
| Temozolomide (long regimen) | 2013 | Phase II | 43 | 5.6 | 9.5 | 35 |
| Motexafin-gadolinium | 2013 | Phase II | 60 | 7.2 | 11.4 | 53 |
| Temozolomide | 2012 | Phase II | 21 | 7.5 | 11.7 | 50 |
| Cisplatin, etoposide, vincristine, ifosfamide | 2010 | N/A | 37 | 4.8 | 13.6 | N/R |
| Targeted therapies | | | | | | |
| Nimotuzumab/EGFR | 2019 | Phase III | 42 | 5.8 | 9.4 | N/A |
| Dasatinib/PDGFRα, crizotinib/c-Met | 2018 | Phase I | 25 | N/R | N/R | N/R |
| Dasatinib/PDGFRα, vandetanib/VEGFR | 2013 | Phase I | 25 | N/R | 15.0 | 52 |
| Nimotuzumab/EGFR | 2014 | Phase II | 44 | N/R | 3.2 | N/R |
| Gefitinib/EGFR | 2011 | Phase II | 43 | 7.4 | N/R | 56.4 |
| Erlotinib/EGFR | 2011 | Phase I | 50 | 1.5/8.0 | 4.1/12.0 | N/R |
| Tamoxifen/estrogen receptor | 2010 | N/A | 31 | 3.9 | 6.3 | 16.1 |
| Bevacizumab/VEGF, Irinotecan/topoisomerase | 2010 | N/A | 12 | 2.25 | 6.25 | 20 |

Source: Tosi U, Souweidane M. Convection Enhanced Delivery for Diffuse Intrinsic Pontine Glioma: Review of a Single Institution Experience. *Pharmaceutics*. 2020, Edison Investment Research. Note: EGFR, epidermal growth factor receptor. PDGFRα, platelet-derived growth factor receptor A. VEGFR, vascular endothelial growth factor

Given the challenging DIPG space, the risk/reward trade-off for under development therapeutics remains high. Therapies showing clinical promise can expect to take a large chunk of the market share; Midatech estimates the addressable market is worth >\$100m worldwide and we expect any approved therapy to take upwards of 50% market share. There are over 70 clinical trials ongoing for DIPG, of which two active trials are in Phase III with headline data expected in 2023 ([nimotuzumab in combination with concurrent radiochemotherapy and temozolomide + valproic acid](#)).

Panobinostat's early promise in DIPG

Panobinostat, the API component of MTX110, is a hydroxamic acid and acts as a non-selective histone deacetylase (HDAC) inhibitor. The drug was approved as an oral chemotherapeutic for relapsed or refractory multiple myeloma in 2015 (in combination with bortezomib and dexamethasone as third-line treatment). It was developed by Novartis and its global rights were acquired by Secura Bio in March 2019. Midatech acquired the rights to develop panobinostat for the treatment of gliomas in June 2017.

In 2015, a multi-centre study led by the Stanford University School of Medicine established the preliminary efficacy of panobinostat in restricting the DIPG tumour growth both in cell lines and in mice xenograft models. The research team screened 14 DIPG cell lines derived from patients'

tumours against 83 available chemotherapy drugs (chosen for their possible effects against brain tumours), exposing cells to small samples of each drug. Of the 83 drugs, only a small number showed promise, of which panobinostat was selected for further study. The study then confirmed the potency and mechanism of panobinostat against DIPG, showing normalisation of tumorigenic changes in the cells and decreased expression of genes associated with cancer cell growth. In mice models too, infusing panobinostat directly into the brain stem slowed tumour growth. These data validate the observation that most DIPG tumours (c 80%) carry the H3K27M mutation in the histone 3.1 or 3.3 genes, which can be effectively targeted by HDAC inhibitors such as panobinostat.

Despite the promise, clinical progression has been hampered by the poor BBB penetration of the currently available oral formulation of panobinostat (bioavailability of c 20%) and the existing drug delivery systems. MTX110, by solubilising panobinostat and employing a CED system, aims to bypass the BBB for direct-to-tumour delivery of the drug. The company asserts that this allows it to deliver panobinostat concentrations of 100,000x as compared to oral administration of the drug, thereby increasing its potential efficacy multi-fold.

Delivered through a CED system

CED is a technique designed to deliver drugs directly into the tumour at high concentrations by entirely bypassing the BBB. Using a CED system, therapeutic agents are introduced directly into brain parenchyma via surgically implanted catheters connected to low-rate infusion pumps. This system allows for delivery of high-concentration payloads directly to the tumour while minimising systemic exposure and toxicity. Unlike other diffusion systems, the CED delivery uses a pressurised pump to deliver the drug to the tumour, increasing its distribution across the tumour rather than just the site of the infusion. Drugs being studied for delivery through CED include conventional chemotherapy drugs, novel small molecule agents, large-molecule antibodies, immunotoxins and viral vectors, which otherwise may not be able to gain access to the brain.

While this technique has been studied for nearly two decades, it remains investigational, as no therapeutics have been approved for infusion directly into brain tissue. The application of a CED system, therefore, may not be a straightforward undertaking, with various variables at play (such as catheter design, placement, drug infusion modalities, etc). Midatech has been experimenting with multiple CED systems as part of its clinical trials: while [the Phase I clinical trial](#) conducted by the University of California San Francisco (UCSF) used a single catheter system by Brainlab (considered to be highly onerous due to the need for surgical insertion during each treatment cycle), another [Phase I trial](#) being conducted by the Columbia University Medical Center is using an implantable continuous flow device by Medtronic. Four trials are ongoing, assessing CED systems as drug delivery mechanisms in DIPG, of which MTX110 seems to be at the most advanced stage (Exhibit 14).

Exhibit 14: DIPG trials using CED systems for drug delivery

| Intervention | Sponsor | Study ID | Status | Study initiation/ completion date | Study design |
|--|--|-----------------------------|---------|-----------------------------------|---|
| CED of chemotherapeutic Irinotecan Liposome Injection | UCSF, The V Foundation for Cancer Research, Pacific Paediatric Neuro-Oncology Consortium | NCT03086616 | Phase I | October 2017/ September 2021 | CED of chemotherapeutic drug Nanoliposomal irinotecan (nal-IRI) given directly into the tumour (19 participants) after completion of radiotherapy. CED will be performed every 4–8 weeks. Drug concentration will start at 20mg/ml and escalate up to 40mg/ml concentration |
| CED of monoclonal antibody Omburtamab | Y-mAbs Therapeutics, Weill Medical College of Cornell University, Johns Hopkins University | NCT01502917 | Phase I | December 2011/ December 2021 | CED of radiolabeled monoclonal antibody Omburtamab given directly into the tumour (64 participants) after completion of radiotherapy |
| CED of chemotherapeutic, solubilised panobinostat (MTX110) | Midatech, UCSF, Pacific Paediatric Neuro-Oncology Consortium | NCT03566199 | Phase I | May 2018/ March 2021 | CED of chemotherapeutic solubilised panobinostat (MTX110) given directly into the tumour (7 participants) after completion of radiotherapy. Courses repeat every 4–8 weeks for up to 24 months in the absence of disease progression or unacceptable toxicity |
| CED of chemotherapeutic, solubilised panobinostat (MTX110) | Midatech, CUMC | NCT04264143 | Phase I | March 2020/ February 2022 | CED of chemotherapeutic solubilised panobinostat (MTX110) and Gadolinium given directly into the tumour (9 participants) over 9–11 days |

Source: clinicaltrials.gov

MTX110 Phase I data positive

Midatech released interim headline data from its Phase I study (conducted by UCSF) in October 2020, meeting its primary endpoint in terms of safety and identifying an optimal dose (between 60µM and 90µM) of MTX110 for its upcoming Phase II study. While survival was not an endpoint for the UCSF study, initial data from the cohort of the seven study participants (enrolled between May 2018 and March 2020) were encouraging; median OS based on Kaplan Meier analysis was 26.06 months (CI 11.3–26.06 months) versus 10 months following standard of care radiation therapy. OS at 12 months stood at 71.4% (five of seven patients alive) versus an average of c 30% historically. The results are one of the best seen in past clinical trials. In comparison, a 2017 clinical trial (Phase I) assessing [CED delivered chemotherapy drug carboplatin for DIPG](#) in 13 children reported median progression-free survival of 13 months and median OS of 15.3 months.

Some concerns remain

The Phase I data keep us cautiously optimistic about the prospects of MTX110, although given the small sample size, the results would need to be replicated in larger clinical trials to establish the efficacy. The Phase II trial is expected to start in H122 evaluating OS at 12 months as the primary endpoint in 21 evaluable patients. Its orphan drug status should allow to company to apply for a fast-track approval and a potentially faster market entry provided supportive Phase II data is obtained. On the other hand, however, ongoing disagreement with Secura Bio ([following its June 2020 termination of the panobinostat licence](#)) is concerning, although Midatech has reassured that the licence termination does not affect the research programme but may cause a delay in the commercialisation of MTX110 for DIPG (post Panobinostat's patent expiry in 2026).

Opportunity beyond DIPG

In addition to DIPG, Midatech is also exploring MTX110's application in other brain tumours such as medulloblastoma and GBM. Medulloblastoma is another type of brain cancer (originating in the cerebellum) with similar incidence as DIPG (300–400 cases annually in the US), albeit with a much better prognosis. It largely afflicts children (accounting for c 75% of cases). Although the current treatment algorithm (surgical resection followed by craniospinal radiation and/or chemotherapy) is successful in achieving remission (five-year survival rate is 80% in children and 60% in adults), the cancer recurs in c 20% of the cases. MTX110 will be targeting this population of recurrent medulloblastoma cases. The company is undertaking a pilot Phase I study with the University of

Texas Health Science Center using a different infusion device into the fourth ventricle. The study is expected to complete by end 2022. Midatech estimates the medulloblastoma market opportunity to be the same as DIPG (\$100m). Another indication, which could be a much larger opportunity for the company, is GBM. Latest figures from the American Cancer Society peg the incidence of brain and other nervous system cancer in the United States at 24,530. The corresponding figure stands at 64,600 for Europe and 156,200 for Asia. More than half of these are GBM cases. 120,000 deaths per year globally are attributed to GBM, highlighting the aggressive nature of the cancer. According to Global Data, the GBM therapeutics market is expected to grow from \$662m in 2017 to \$1.4bn in 2027 across the US, EU5, Japan and China at a CAGR of 7.5%. MTX110 will be targeting an undisclosed subset of GBM patients.

MidaCore: Gold nanoparticles

The MidaCore technology platform uses ultra-small gold nanoparticle drug conjugates (2–4nm in size) to improve biodistribution of drugs and aid in targeted drug delivery. Each nanoparticle (gold core stabilised with a carbohydrate coating) can be linked to multiple therapeutic agents (ranging from small molecules to monoclonal antibodies) and their small size allows for targeted delivery even in areas that are difficult to reach, such as across membranes and between cells. The MidaCore pipeline is limited to MTX114, a formulation of methotrexate as topical treatment for psoriasis. With Midatech's resources focused towards MTX110 and the Q-Sphera portfolio, we expect a comparatively slower pace of development work on MTX114.

Sensitivities

Midatech is subject to the usual risks associated with drug development – clinical development (delays or failures), competitor successes, partnering setbacks, financing and commercial risks – although regulatory risks are somewhat mitigated as the underlying APIs for the company's formulations are typically already approved and marketed. Execution on its pipeline assets will be a key factor in determining the company's future outlook and direction. Midatech has had some setbacks in the past on this front, the most recent being the termination of its then lead Phase I programme, MTD201/Q-Octreotide, and closure of its Bilbao, Spain, manufacturing facility in March 2020 due to financing related challenges. While the realigned focus on broadening the portfolio and employing a pure-play out-licensing strategy mitigates some of these risks, the ability to generate market interest in its platforms and get partners on board will be crucial to the company's development plans. While the MTD201 trial data offer some validation to Midatech's Q-Sphera technology, the PLGA microsphere technology has been available in the market for a number of years and may be challenged by newer, more advanced drug delivery systems such as nanoparticles. Q-Sphera operates in a competitive space with a number of highly differentiated alternative technologies vying to deliver similar outcomes (in particular, nanoparticle-based technologies).

Clinical trial delays (either due to funding or administrative issues) are another risk that could affect launch dates and sales potential. Midatech management has indicated it may apply for an accelerated approval following Phase II studies in DIPG, given the orphan drug designation. The need for further trials beyond those planned, or unexpected delays, could also affect the time to market and/or funding need for the asset.

Funding is an ever-present risk given the nascent pipeline and limited probability of break-even in the near term. While the recent £10m fund-raising has eased the funding situation and may extend the cash runway into 2023, further funds may be required for progressing MTX110's clinical programme. While Midatech's new business strategy calls for partnered development of assets, there is limited visibility on the potential timing and terms for the planned out-licensing of the in-

house development projects. Successful execution of a deal will depend on a multitude of factors, primarily the strength of the study data.

Given the lead asset MTX110 targets the highly risky brain cancer space (where there is a very low success rate of approval) and the Q-Sphera pipeline is at a very early stage of development, portfolio risk remains high. This could ease out as the pipeline progresses to the clinic.

Financials

Following the sale of its US commercial assets in 2018, Midatech has had to fund its operations largely through equity issues (the exception here is the c £6m Spanish government loan received in 2017). Since 2019, Midatech has raised c £35m in equity, including the £8m strategic investment by CMS Medical Venture in February 2019, which saw the group take a controlling 51% stake in the business (although the holding has diluted down to 10.6% following subsequent equity issues). In 2020, the company raised a further c £10m (from two equity issues), although a portion of it was used to pay down the c £6m Spanish government loan. Following the 2020 strategic review, Midatech's leaner organisational setup has allowed it to have a stronger control on its cash burn (£2.2m in H220 versus £6.8m in 2019) and the reported net cash balance of £3.4m (cash of £4.2m less lease liabilities of £0.8m) at end-H121 supported by another £10m equity issue in July 2021 (pro forma cash of c £13m) could extend its cash runway to 2023 assuming cash burn rates remain similar to recent levels. This should be sufficient to commence a Phase II trial for MTX110 and progress the Q-Sphera pipeline. Operationally, the FY20 results were affected by the restructuring and strategic alignment of the business. Midatech reported an operating loss of £23m (versus £11.3m in FY19) but this figure was affected by a £12.4m non-cash impairment charge related to MTD201 and the Spanish manufacturing facility as well as related redundancy and legal costs (an additional £4.5m per our estimates). The normalised operating loss was £10.7m, slightly lower than the previous year figure. The H121 results reflect a more sustainable financial matrix for the company – the normalised operating loss more than halved to £3.06m from £6.75m in H120, driven by a c 50% reduction in R&D expenses (£2.01m; £3.99m in H120) and a 44% reduction in administrative expenses (£1.64m; £2.93m in H120) following the business realignment.

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