Zacks Small-Cap Research

November 27, 2017
David Bautz, PhD
312-265-9471
dbautz@zacks.com

scr.zacks.com
10 S. Riverside Plaza, Chicago, IL 60606

Midatech Pharma Plc

MTP – Nasdaq

MTP: Initiating Coverage of Midatech Pharma; Novel Nanotechnology Platforms Focused on Oncology and Other Therapeutic Areas…

Based on our probability adjusted DCF model that takes into account potential future revenues from GNP, Q-Sphera, and NI platform products along with revenues from Midatech Pharma US, MTP is valued at $6.50 per share. This model is highly dependent upon continued clinical and commercial success and will be adjusted accordingly based upon future clinical results and the company's execution.

Current Price (11/27/2017)	$1.36
Valuation	**$6.50**

INITIATION

Midatech Pharma Plc (MTP) is an international oncology focused specialty pharmaceutical company with three novel micro- and nanotechnology platforms: Gold nanoparticles (GNP) for targeted delivery, Q-Sphera for sustained release (SR) applications, and Nano Inclusion (NI) for local delivery. The technologies are designed to re-engineer and reformulate existing therapeutic drugs, thus decreasing regulatory risk, with the aim of improving safety, efficacy, and biodistribution parameters of the agents.

MIdatech has a number of potential value drivers over the next 18 months, including a first-in-human bioequivalence study of Q-Octreotide (MTD201), an initial clinical trial of MTX110 in childhood glioma, and the initiation of the clinical program for MTD119 in hepatocellular carcinoma (HCC). With an established oncology supportive care sales channel, Midatech could be in a position to launch its own products in 2020.

SUMMARY DATA

52-Week High	**$3.65**
52-Week Low	**$1.00**
One-Year Return (%)	**-50.81**
Beta	**N/A**
Average Daily Volume (sh)	**8,810**
Shares Outstanding (mil)	**N/A**
Market Capitalization ($mil)	**$30**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**81**
Insider Ownership (%)	**5**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using #Lin Estimate	**N/A**
P/E using #Lin Estimate	**N/A**

Risk Level	**N/A**
Type of Stock	**Large-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(In millions of £)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	1.8 A	2.0 A	1.4 A	1.4 A	5.6 A
2017	1.5 A	1.9 A	2.0 E	2.0 E	7.4 E
2018					9.0 E
2019					10.7 E

Earnings per share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	-£0.61 A	-£0.70 A	-£0.95 A	-£1.20 A	-£0.56 A
2017	-£0.09 A	-£0.10 A	-£0.06 E	-£0.07 E	-£0.31 E
2018					-£0.24 E
2019					-£0.24 E

© Copyright 2017, Zacks Investment Research. All Rights Reserved.

WHAT'S NEW

Initiating Coverage

We are initiating coverage of Midatech Pharma Plc with a $6.50 valuation. MIdatech is a U.K. based international specialty pharmaceutical company focused on oncology and other therapeutic areas. The company has three proprietary drug delivery technologies: Q-Sphera for sustained release of already marketed products, Midacore gold nanoparticles (GNP) for targeted delivery, and Nano Inclusion (NI) for local delivery. The Q-Sphera technology involves the consistent and precise encapsulation of active drug compounds within polymer microspheres. The microspheres are engineered to release the drug compound into the body in a controlled and consistent manner over an extended period of time. The GNP technology was developed for repurposing and improving key parameters of new and existing drugs, including how the drug is distributed in the body and targeting to specific tissues. The NI technology is utilized to enhance solubility to allow for localized delivery. Each platform has the capability to be used in a variety of disease areas including oncology, immunology, and neurology. Midatech currently has three lead compounds in development:

- **MTD201 (Q-Octreotide)**: Octreotide is an existing product administered by injection for controlling the production of growth hormone in people suffering from acromegaly. It is also a treatment for carcinoid syndrome from the occurrence of neuroendocrine tumors (NET; tumors that secrete hormones). Midatech is developing a sustained release version of octreotide ("Q-Octreotide") that will compete with the market leader Sandostatin® LAR® (sold by Novartis). Midatech is planning an initial human bioequivalence study of MTD201 in 24 subjects, which will be followed by a confirmatory study in 76 patients. We anticipate the initial study beginning in the fourth quarter of 2017 or first quarter of 2018 with topline data available in the first half of 2018.

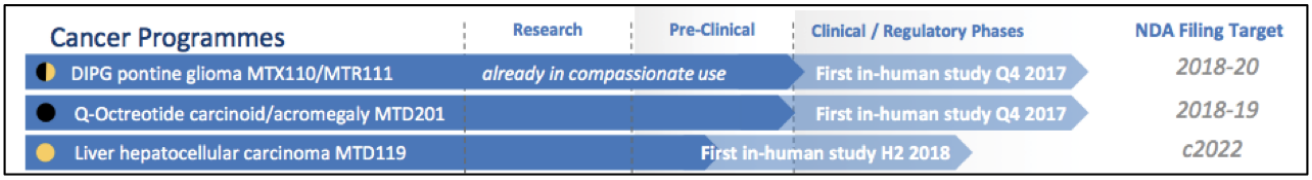
- **MTX110**: This is a formulation of panobinostat (already approved for treatment of multiple myeloma) that utilizes Midatech's NI technology to enhance solubility and allow localized delivery. The company is developing MTX110 for the treatment of diffuse intrinsic pontine glioma (DIPG), an ultra-rare pediatric cancer of the brain stem. Thus far, five patients have been treated through a compassionate use protocol, and Midatech is planning to initiate a formal clinical trial in early 2018.

- **MTD119**: This is a GNP construct that utilizes cytotoxic DM1 (which is used in an approved antibody-drug conjugate). Midatech is developing MTD119 for the treatment of hepatocellular carcinoma, an orphan indication with a total market size forecast to reach $1 billion in 2024. Preclinical studies show that GNP conjugation allows otherwise lethal doses of DM1 to be administered, which results in peak tumor growth reduction more than six times the current standard of care (sorafenib). IND enabling studies are initiating with a first-in-human study planned for late 2018 or early 2019.

Midatech has a number of value drivers over the next 18 months as the company moves its lead products into the clinic. Both MTD201, which is being developed along the 505(b)(2) submission pathway, and MTX110, which is targeting an ultra-rare indication, could potentially move from the clinical to commercialization in a short time frame. In addition, MTD201 is relatively de-risked from a regulatory viewpoint as octreotide is already approved and data up to this point shows strong equivalence between MTD201 and the Sandostatin® LAR® reference. The company is further differentiated by its existing U.S. sales force, which could help the company to quickly capitalize on an approved product by seamlessly integrating it into the sales infrastructure without the need to sign a partnership with a larger biopharmaceutical company. Lastly, without the need for a commercialization partner, Midatech stands to potentially realize the full value of each of the development products.

INVESTMENT THESIS

Midatech Plc is a specialty pharmaceutical company with three novel drug delivery technologies. The technologies are designed to enable the targeted delivery, sustained release, or solubilized local delivery of existing therapeutic drugs. The Q-Sphera sustained release (SR) technology platform, with numerous and distinct advantages over traditional polymer microsphere production, utilizes precisely and consistently manufactured monodispersed micro particles such that active drug compounds are released into the body in a tightly controlled manner over an extended period of time (e.g., weeks to months) The gold nanoparticle (GNP) technology platform is based on GNP drug conjugates, which at 2 nm are among the smallest particles in biomedical use. They are composed of a core of gold atoms surrounded by a layer of carbohydrates and linkers for attachment of small molecules (e.g., chemotherapeutics, peptides, etc.) and targeting agents. The small size and multivalency arrangement around the gold core underpin the ability to improve biodistribution and thus safety and efficacy of existing drugs. Midatech's Nano Inclusion (NI) technology is utilized for potent small molecule chemotherapeutics that have minimal solubility at biological pH, which limits them to oral administration. When reformulated with the NI technology, the complexed molecules solubilize such that parenteral routes of administration can be employed. This enables local administration directly into the tumor. The company's three lead compounds are each expected to enter the clinic over the next 12-18 months.



Source: Midatech Plc

TECHNOLOGIES

Q-Sphera: Sustained Release Technology

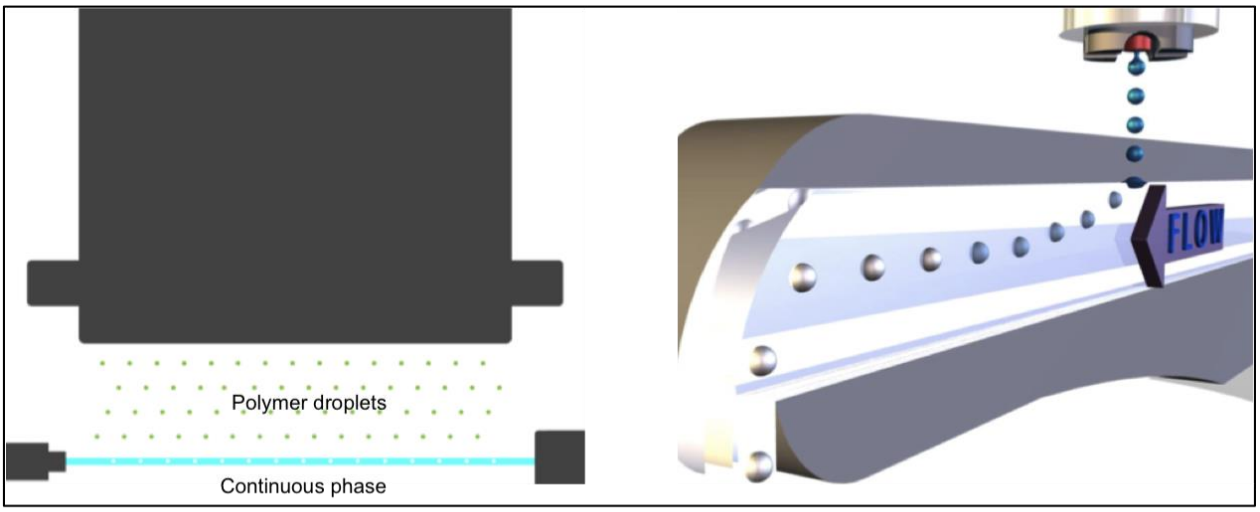
The ability to improve dosing, lower toxicity, and decrease the overall risk associated with pharmaceutical treatments is an important area of research. An inability to control these factors leads to a number of pharmaceuticals (both small molecules and proteins) being abandoned or limiting their commercial success when approved. Many of those factors have to do with dosing of pharmaceuticals and an inability to either control drug exposure or a necessity for overly burdensome dosage schedules. Over the past 30 years, a large amount of research has been conducted on the use of biodegradable polymers for controlled drug delivery. These polymers can be used to both improve dosing (e.g., slow release dosing vs. repeated parenteral administration) and increase safety by tightly regulating the amount of drug in a patient's system at one time.

The Q-Sphera platform was designed to address several problems associated with the microencapsulation and polymer-depot based drug delivery. The approach MTP takes is unusual in that it does not rely on solvent evaporation. Instead, a solvent extraction method is utilized. The key advantage that the Q-Sphera approach offers is product monodispersity. Very tight particle size distributions can be produced, which increases the usable product yield. Emulsion processes such as those used to manufacture Sandostatin® LAR®, are more wasteful in that they produce large quantities of unusable particles (i.e., either too large or too small). Additionally, these emulsion processes use large volumes of unfavorable organic solvents (such as ethyl acetate and dichloromethane). Particles produced from these solvent solutions must be rigorously washed to remove residual traces of solvent.

The Q-Sphera approach to forming particles by "desolvation" is applicable to many polymer types, however as PLGAs are ubiquitous in drug-delivery, MTP formulation work has concentrated on these materials. The polymers Midatech uses most frequently are linear poly-esters of lactic (PLA) and glycolic acids (i.e., polylactide-co-glycolide, [PLGA]) that are insoluble and unstable in water due to simple hydrolysis. Each of these can be processed into any shape or size and they are soluble in a wide range of solvents. In addition, the rate of drug release can be easily controlled through altering the physico-chemical properties of the polymer(s). In the body, hydrolysis is the dominant mechanism for the controlled degradation of the polymer microparticles. This is also the reason that the microspheres cannot be provided as a pre-mixed, ready-to-use suspension product. They must be stored dry, (i.e., freeze-dried) to remove traces of water.

Midatech have shown that the encapsulation process is compatible with many classes of therapeutics, small molecules, and peptides, including octreotide, cyclosporine, leuprolide (and several related GnRHR agonists), exenatide, P9, AGN-3, and small molecules dexamethasone, PP-001, tivozanib, and dithranol. The majority of Midatech's SR products have required formulations that release drug payloads over 1 or 3 months.

The following figures shows how the Q-Sphera system works. The figure on the left shows how a solution of polymer (typically PLA or PLGA) and solvent mixed with the drug to be encapsulated is emitted from a piezo device to form droplets (typical size of a drop is 40-150 picoliters). Droplet ejection is caused by electrical excitation of a piezo-electric crystal, which contracts upon application of a voltage. Midatech's current technology allows up to 6,000 droplets per second from a nozzle (6 kHz). Midatech's current array manufacturing method produces 6 MHz per head per second. There are 512 heads in the array equipment, hence generating 6 kHz x 512 heads = 3,072,000 droplets per second. The figure on the right shows the droplets falling into a 'continuous phase', which removes the solvent of the droplets and forms solid microspheres. The anti-solvent is a critical component in the Q-Sphera system. Its purpose is to rapidly extract the solvent from the droplets of polymer solution ejected from the piezo-device. In order to effect rapid extraction, the anti-solvent must be largely miscible with the solvent.

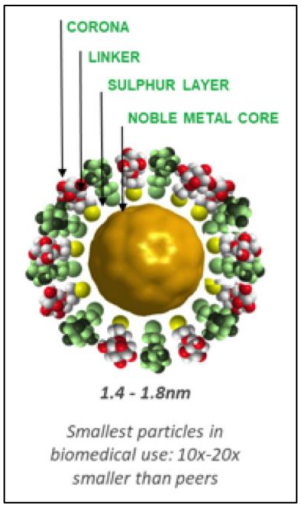


Source: Midatech Plc

Gold Nanoparticle Technology

Midatech's gold nanoparticle (GNP) design and synthesis technology enables the production of stable, reproducible constructs consisting of 1-2 nm sized metallic cores that are stabilized by a strongly bound field of thiolate ligands. The GNP technology is focused on the targeting of individual tumors with specific targeting agents and delivering a therapeutic payload into the tumor cell, all while decreasing the side effect profile associated with off-target effects of chemotherapy.

GNPs are comprised of a core of gold atoms (approximately 100 gold atoms per GNP) surrounded by an organic layer of carbohydrates (e.g., glucose, galactose, or lactose) attached via gold-sulfur bonds that stabilizes the metallic core and makes the particle water-soluble and biocompatible. Metals such as gold are electronegative, thus enabling a strong attraction between the gold atom and the electron-rich sulfur atom. GNPs are typically less than 2nm in size, and 8nm if fully functionalized, which is roughly five- to ten-fold smaller than any other delivery vehicle in clinical trials. A cartoon representation of GNPs is shown to the right.



Source: Midatech Pharma Plc

GNPs have a number of key advantages in their use as drug delivery vehicles, driven chiefly by their small size and multivalency attributes:

Multivalency:

- Targeting: multivalency - enables binding of several targeting and therapeutic agents to a single nanoparticle
- Therapeutics: active payloads conjugated to form small (~5nm) medicines for targeted delivery

- Solubility: enable the transport of water insoluble and lipid soluble compounds to disease sites
- Releasability: designed to release the active compound inside the cell

Size:

- Mobility: small size (~1.5 nm) and defined charge allows transport to disease sites otherwise very difficult to reach
- Compatibility: ultra-small gold nanoparticles are bio-inert, non-toxic, non-immunogenic, and do not generate an immune response
- Excretability: drug conjugates eliminated via the kidneys and liver

It is believed GNP's nondisruptively penetrate the cell membrane to deliver drugs. The underlying mechanism of how GNPs can nondisruptively passage cell membranes can be via endocytosis (entrance) or exocytosis (exit). Endocytosis of GNP's enables more efficient intracellular drug-delivery, while exocytosis allows more clearable delivery after drug delivery. Endocytosis can involve receptor mediated endocytosis, phagocytosis, macropinocytosis, and pinocytosis – depending on the functionalized payload(s) and/or corona. Endocytotic efficiency of GNP's is dependent on the physicochemical properties such as size, shape, and surface chemistry, as well as cell type. Due to their size and spherical shape, Midatech GNP's appear to enter and exit the cell efficiently (compared to larger or cylindrical particles). Positively charged GNP's exhibit much higher rates of endocytosis than negatively or neutrally charged GNP's, and they seem to remain in the cell longer.

Intracellular release of payloads is via glutathione (GSH)-mediated release of payloads from the GNP surface. GSH is the most abundant thiol species in the cytoplasm and the major reducing agent in biochemical processes, providing a potential *in situ* releasing source in living cells. The intracellular GSH concentration (1-10 mM) is substantially higher than extracellular levels (2 μM in plasma), providing a mechanism for selective intracellular release. GSH thus serves as an effective trigger to release a payload from GNP surfaces. In oncology, the difference in GSH concentrations is even more marked between cancer cells and normal cells, thus it is an important advantage in GNP cancer therapeutics.

Nano Inclusion Technology

Many of the small molecule chemotherapeutics that are indicated for solid tumor treatment have minimal solubility in water or aqueous buffers at biological pH. This can limit the available routes of administration for a drug. In some cases, the problem of insolubility can be addressed by formulation in mixtures of water and a biocompatible solvent such as ethanol or dimethyl sulfoxide (DMSO). However, for the treatment of brain cancers (e.g., glioma) local infusion of a solvent is undesirable. Midatech has investigated nano approaches for increasing the aqueous solubility of several classes of small molecule cancer therapeutics, involving complexes that solubilize these agents and enable parenteral administration directly into tumors.

The complexes comprise a hydrophobic inner surface and a hydrophilic outer surface, and as a result are capable of forming host-guest complexes. A hydrophobic, poorly water-soluble small molecule drug can associate with the inner, more hydrophobic surface of the host ring, while the larger hydrophilic outer surface remains solvated by water molecules. Such complexes can be particularly stable, depending upon the strength of the host-guest interaction. The key advantage of host-guest complexation is a significant increase in the aqueous solubility of the guest compound at biological pH.

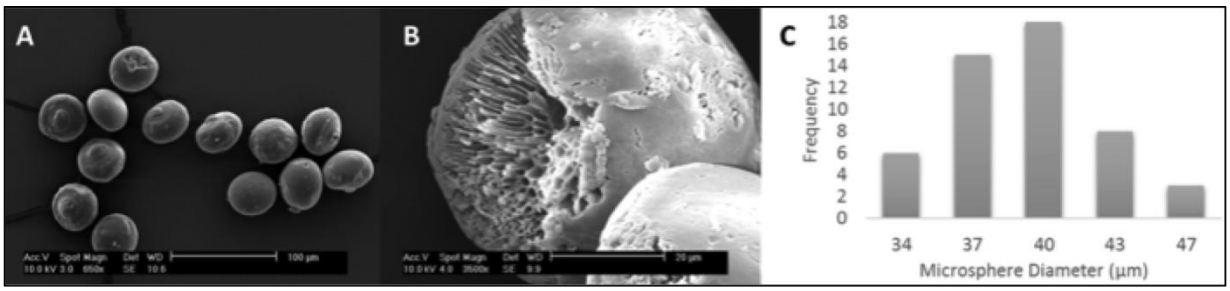
Midatech has studied the complexation and solubility-enhancing effects of these nano complexes on the histone deacetylase inhibitor class of chemotherapeutics. The first successful host-guest formulation is MTX-110, a water-soluble complex panobinostat for the treatment of brain cancer. The resulting complex is readily soluble in water at millimolar concentrations and is stable at room temperature for at least 24 weeks, thus enabling parenteral administration routes directly into the tumor that otherwise would not be possible.

LEAD DEVELOPMENT PRODUCTS

MTD201 (Q-Octreotide)

Midatech's lead development product, MTD201 (Q-Octreotide), is based on the company's SR polymer microsphere technology (Q-Sphera). The microspheres are small (approximately 25 μm), spherical particles that are designed for the sustained release of peptides and other small molecule drugs. Midatech's manufacturing process allows for high drug loading, precise control over particle size and morphology, and highly linear reproducible drug release kinetics. The particles can be injected using a very fine gauge needle with clear benefit

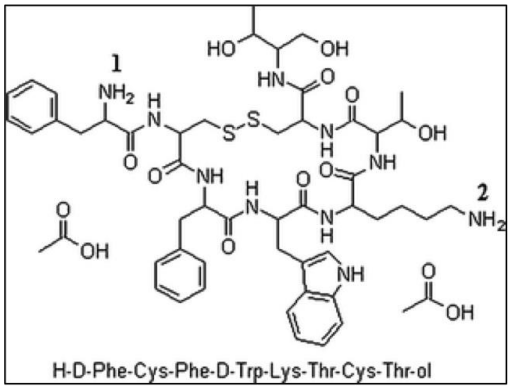
for the patient. The following image shows the MTD201 microspheres at two different magnifications (A and B) as well as a histogram of the microsphere diameters (C) showing an impressively narrow range of sizes.



Source: Palmer *et al*., 2017

Sandostatin®

Octreotide is an octapeptide that mimics naturally occurring somatostatin, although it is a more potent inhibitor of growth hormone, glucagon, and insulin. Ultimately, the drug causes a normalization of growth hormone and/or insulin-like growth factor 1 (IGF-1). It is an existing, immediate- and sustained- release injection product used to decrease the production of growth hormone in people suffering from acromegaly and for the treatment of neuroendocrine (hormone secreting) tumors (NET). It is sold by Novartis under the brand name Sandostatin® and the sustained release version Sandostatin® LAR®. Patients begin treatment with Sandostatin® injected subcutaneously three times a day for two weeks followed by Sandostatin® LAR® administered intramuscularly once every four weeks. The structure of octreotide is shown below.



Source: Ghassemi *et al*., 2012

Following subcutaneous injection, Sandostatin® is absorbed rapidly with peak plasma concentrations 0.4 hours after dosing and a half-life of 1.7 hours (Sandostatin® prescribing information). Sandostatin® LAR® consists of microspheres of the biodegradable polymer poly lactic-co-glycolic acid (PLGA). Peak serum concentration is within 1 hour of administration, which then slowly declines over 3-5 days before slowly increasing and reaching a plateau approximately 2-3 weeks following injection.

Acromegaly

Acromegaly is a hormonal disorder caused by excessive production of growth hormone during adulthood. This results in an increase in bone size in the hands, feet, and face. It typically affects middle-aged adults and is usually not recognized immediately, however if not treated it can lead to serious illness that can potentially become life threatening. Initial symptoms of acromegaly are enlarged hands and feet (e.g., a ring no longer fits or an adults shoe size has progressively increased). Additional symptoms include gradual changes in the shape of the face, an enlarged nose, thickened lips, and increasing space between the teeth.

Morbidity and mortality rates are high in those with acromegaly, typically due to associated cardiovascular, cerebrovascular, respiratory disorders, and malignancies (Berg *et al*., 2010). For acromegaly caused by pituitary tumors (which account for over 95% of cases), trans-sphenoidal surgery is the first line treatment (Bush *et al*., 2008). This is curative in approximately 50-60% of cases. For those with persistent acromegaly, somatostatin analogues are the preferred therapy, particularly since the long-acting formulations limit treatment to just once a month.

Sandostatin® LAR® was tested in three clinical trials in acromegalic patients. The following table shows results for 122 patients who received 12 injections of Sandostatin® LAR®, showing that 2/3rd of patients had growth hormone levels reduced to <5.0 ng/mL and a normalization of IGF-1 levels.

Mean Hormone Level	Sandostatin Injection S.C.		Sandostatin LAR Depot	
	n	%	n	%
GH <5.0 ng/mL	116/122	95	118/122	97
<2.5 ng/mL	84/122	69	80/122	66
<1.0 ng/mL	25/122	21	28/122	23
IGF-1 normalized	82/122	67	82/122	67
GH <5.0 ng/mL + IGF-1 normalized	80/122	66	82/122	67
<2.5 ng/mL + IGF-1 normalized	65/122	53	70/122	57
<1.0 ng/mL + IGF-1 normalized	23/122	19	27/122	22

[1]Average of monthly levels of GH and IGF-1 over the course of the trial

Source: Sandostatin® LAR prescribing information

Acromegaly is considered an orphan indication as it only affects approximately 20,000 individuals in the U.S., with approximately 1,000 new cases diagnosed each year (Holdaway *et al*., 1999). In 2016, Novartis reported approximately $1.6 billion in revenues for Sandostatin® LAR®. In addition to Sandostatin®, Somatuline® is sold by Ipsen, which generated €538 million in 2016 revenues, and Somavert® is sold by Pfizer, which generated $232 million in 2016 revenue (EvaluatePharma). If Midatech was able to achieve only 5% of the acromegaly market (which totals approximately $2.2 billion), that would represent an approximately $100 million opportunity.

Neuroendocrine Tumors and Carcinoid Syndrome

Sandostatin® LAR® is used to treat NETs and symptoms associated with endocrine tumors such as carcinoid syndrome. NETs are slow growing tumors that arise from neuroendocrine cells. They can be either "non functioning", in which they lack hormone production, or "functioning", in which the tumor produces an abundance of bioactive hormones leading to carcinoid syndrome. Signs and symptoms of carcinoid syndrome include flushing of the face, severe diarrhea, and asthma attacks (Bendelow *et al*., 2008).

Somatostatin analogues are used to treat advanced NETs of the midgut or unknown primary tumor location, and control the hormone related side effects of inoperable carcinoid tumors with features of the carcinoid syndrome. (Narayanan *et al*., 2016). The following table shows the results of a six-month clinical trial in which patients with carcinoid syndrome were treated with Sandostatin® LAR®. The results showed a decrease in the number of daily stools and daily flushing episodes.

Treatment		Daily Stools (Average Number)		Daily Flushing Episodes (Average Number)	
	n	Baseline	Last Visit	Baseline	Last Visit
Sandostatin Injection S.C.	26	3.7	2.6	3.0	0.5
Sandostatin LAR Depot					
10 mg	22	4.6	2.8	3.0	0.9
20 mg	20	4.0	2.1	5.9	0.6
30 mg	24	4.9	2.8	6.1	1.0

Source: Sandostatin LAR prescribing information

In addition to treating the symptoms, treatment of patients with metastatic gastroenteropancreatic neuroendocrine tumors with Sandostatin® LAR® resulted in an increase in median time to tumor progression (14.3 vs. 6 months; HR=0.34) and an increase in stable disease at six months (66.7% vs. 37.2%) when compared to placebo treatment (Rinke *et al*., 2009).

Clinical Development Plan

On September 4, 2017, Midatech announced the submission of a clinical trial application (CTA) for a first in human pivotal study of MTD201 comprising an exploratory phase in 24 healthy volunteers, followed by a confirmatory phase in an additional up to 76 subjects, giving an expected total of 100 subjects for the study. The company is

hoping to show interchangeability with Sandostatin® LAR® both pharmacokinetically and pharmacodynamically, thus potentially offering patients an alternative treatment for NETs, carcinoid syndrome, and acromegaly. We anticipate initial data late in the first quarter or early in the second quarter of 2018. Assuming positive clinical results, the company plans to file for approval under the 505(b)(2) pathway.

MTX110

MTX110 is being developed for the treatment of diffuse intrinsic pontine glioma (DIPG), and uses the company's NI technology, which allows for the solubilized local delivery of potent therapeutics directly to the tumor. The active compound is the poorly soluble hydroxamic acid drug panobinostat, a histone deacetylase inhibitor (HDACi), which until recently could not be formulated for parenteral administration. Midatech's NI technology enabled the aqueous solubility of this class of small molecule cancer therapeutic, which expands parenteral delivery options that in turn are expected to improve the safety and efficacy of the treatment. Midatech in-licensed the drug panobinostat for use in treating DIPG for an upfront payment of $1 million and potential future milestone payments. Panobinostat was developed by Novartis and approved in 2015 for the treatment of multiple myeloma.

DIPG

DIPG is a highly infiltrative brainstem high grade glioma that occurs mostly in children. The tumors are aggressively infiltrative such that cancer tissue typically cannot be differentiated from normal brain tissue. The overall median survival of children with DIPG is approximately 9 months, and remains unchanged despite decades of clinical trial research. The only standard of care is palliative focal radiotherapy, but this has minimal effect on survival and essentially all children die of this disease. Surgical resection is unavailable due to the location of the tumor in the brainstem. New therapeutic strategies are urgently needed. Approximately 1,000 individuals worldwide are diagnosed with DIPG each year.

Panobinostat

Panobinostat (Farydak®) is a potent, nonselective histone deacetylase inhibitor. It was selected as a potential treatment for DIPG following the screening of 83 drugs against 14 patient-derived DIPG cell cultures (Grasso *et al.*, 2015). The drugs were selected by pediatric neurooncologists as either promising targeted agents or traditional chemotherapeutic agents used in pediatric brain tumor therapy. Panobinostat was effective against 12/16 patient-derived DIPG cell cultures. Although effective in both *in vitro* and *in vivo* models, panobinostat does not cross the blood-brain barrier effectively thus necessitating an alternate means of delivery. Direct delivery of MTX110, the soluble form of panobinostat, bypasses the blood brain barrier and ensures adequate drug exposure to tumor cells. MTX110 molecular targeting and intratumoral delivery provides significant potential for treatment of DIPG.

Convection-Enhanced Delivery

One of the many difficulties in treating tumors of the central nervous system is getting enough drug into the tumor for a sufficient time to allow for a therapeutic effect. Many drugs do not effectively pass through the blood-brain barrier, and for these compounds direct injection into the tumor is commonly used. However, even with direct administration, limited diffusion of drug through the tumor and brain interstitium means only a small volume of tissue surrounding the injection site is effectively treated.

Convection-enhanced delivery (CED) is a method used to deliver drugs into the brain through a pressure gradient in order to saturate the extracellular fluid compartment (Bobo *et al*., 1994). In contrast to diffusion, which depends entirely upon a concentration gradient to distribute the molecules, the use of hydraulic pressure in CED allows for homogenous distribution over large distances by displacing the interstitial fluid. Since being shown to be safe for the delivery of drugs to the brainstem (Sandberg *et al*., 2002), CED has been tested in a number of adult malignant gliomas, however there are no completed CED trials for DIPG with a few clinical trials ongoing (Zhou *et al*., 2017).

Clinical Development Plan

Midatech is planning to initiate an open label combined Phase 1/2 clinical trial of MTX110 using CED in DIPG in early 2018 to establish safety, dosage, and efficacy of the treatment. The efficacy endpoint for the Phase II component will be Overall Survival (OS) at 12 months, conducted at the recommended Phase 2 dose. To date, MTX110 has been used on a compassionate use basis to treat five patients, where the drug was well tolerated. Regulators in both the FDA and EU have been supportive of the further development of MTX110, and the Phase I/II study is now required to evaluate efficacy of the drug.

There is a potential for orphan drug designation along with accelerated approval (pending positive data from the Phase 1/2 trial) due to DIPG being an ultra-orphan indication with no other treatment options. Midatech is planning for the study to be concluded during 2019, with a chance for the drug to be on the market in 2020. Treating DIPG represents a potential $50-$100 million worldwide opportunity based on the available patient population and potential for orphan drug pricing.

MTD119

MTD119 is the company's lead development product utilizing the GNP technology. It is being developed for the treatment of hepatocellular carcinoma and utilizes mertansine (DM1) as a cytotoxic agent. DM1 is a derivative of maytansine that is currently utilized in the approved antibody-drug conjugate (ADC) therapy Kadcyla®. In preclinical models, Midatech has reported the GNP-conjugation allows otherwise lethal doses of mertansine to be administered with peak reduction in tumor growth more than 6x greater than the current standard of care, sorafenib (Nexavar®). The company has initiated an IND-enabling program to study drug metabolism, pharmacokinetics, dosing, and toxicity of MTD119 which, if successful, will be followed by a first in human study set to initiate in the second half of 2018 or early 2019.

Liver Cancer

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, with over 700,000 individuals affected worldwide, and is the third leading cause of cancer death in the world (ACS). HCC is relatively rare in the U.S. (approximately 35,000 individuals in the U.S. will be diagnosed with HCC in 2017) and other countries where hepatitis infections are not widespread, as most cases of HCC are due to hepatitis infection (both hepatitis B and C). Most cases of liver cancer in countries with low hepatitis rates are due to metastasis of other primary tumors.

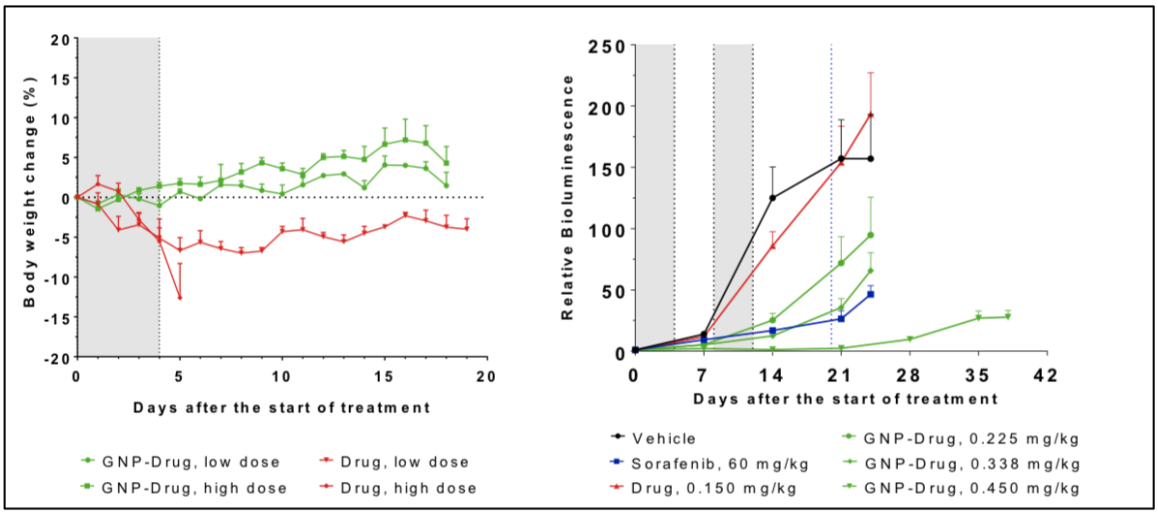
Survival time for patients with HCC is entirely dependent on how advanced the disease is when first diagnosed. If found early, liver transplantation offers a potential curative therapy, with 5-year overall survival of 75% and a tumor recurrence rate of less than 15% (Mazzaferro *et al*., 1996). Patients with small tumors and little underlying cirrhosis are eligible for surgical resection. Additional treatment options include local ablative therapies such as radio-frequency ablation (RFA), trans-arterial chemo-embolization (TACE), percutaneous ethanol ablation, and radioembolization.

There is no cure for advanced HCC; thus, there exists a significant unmet need for an effective therapy. The current standard of care for advanced HCC is sorafenib, which was approved based upon the results of two randomized, double blind, placebo controlled clinical trials where survival was extended by between 2 – 3 months (Llovet *et al*., 2008, Cheng *et al*., 2009). Sales of Nexavar® totaled $963 million in 2016, with approximately 80% of those revenues derived from the treatment of HCC (EvaluatePharma).

For patients refractory to sorafenib, the FDA recently approved regorafenib (Stivarga®) based on the outcome of a Phase 3 clinical trial of 573 patients with HCC that had progressed after treatment with sorafenib (Bruix *et al*., 2017). Similar to sorafenib, regorafenib was shown to extend median overall survival by 2.8 months compared to placebo.

HCC Targeted GNP

A GNP construct for targeting HCC was developed based on a gold nanoparticle core covered with a combination of carbohydrate galactose ligands and the potent tubulin inhibitor DM1 (mertansine), which inhibits microtubule assembly and disrupts mitosis in malignant cells. Preclinical models have shown a clear impact of the GNP technology on the safety and efficacy of DM1. In preclinical safety models, doses achieved with MTD119 (GNP bound DM1) were up to three times higher than those achieved with DM1 alone. The below left figure shows mice treated with DM1 alone at 150 µg/kg tolerated the drug very poorly (as exhibited by weight loss), whereas mice treated with GNP-DM1 at 450 µg/kg tolerated the drug very well (increasing weight during the study). The MTD119 construct was then tested in preclinical efficacy models, where it was tested in animals implanted with human liver tumor cells. The below right figure shows the superiority of MTD119 versus the current standard of care sorafenib, as well as versus DM1 alone. The only group of animals that completed the study was the one treated with high dose MTD119; mice treated with sorafenib or DM1 alone did poorly and did not complete the study. These findings likely reflect the impact the GNP technology has on DM1, including altered biodistribution, targeted efficacy, and reduced off target side effects.



Source: Midatech Pharma Plc

U.S. Commercial Infrastructure

In 2015, Midatech acquired DARA Biosciences, Inc. (now Midatech US), a specialty pharmaceutical company primarily focused on the commercialization of oncology treatment and supportive care pharmaceutical products. The acquisition provided Midatech with a commercial presence in the U.S., which includes field sales representatives and a revenue stream in oncology. Midatech US is currently commercializing the following products:

Zuplenz® (ondansetron): the only FDA approved oral soluble film indicated for chemotherapy induced nausea and vomiting, radiotherapy induced nausea and vomiting, and post operative nausea and vomiting.

Gelclair®: an FDA approved product for the management and relief of pain due to oral mucositis.

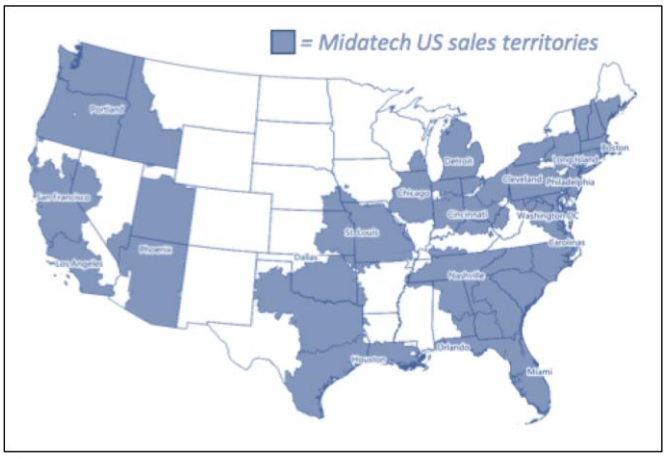
Oravig® (miconazole): an orally dissolving buccal tablet approved for oral thrush

Soltamox®: FDA approved oral liquid solution of tamoxifen citrate, for the prevention of breast cancer

Ferralet® 90: A prescription iron supplement for the treatment of all anemias that are responsive to oral iron therapy

Aquoral: An artificial saliva spray for chemotherapy/radiation therapy induced dry mouth

Midatech US currently has 20 sales representative and 5 field sales managers with access and established relationships in the highest prescribing oncology markets. It is scheduled to become break-even on a standalone basis by early 2018, at which point it will begin contributing to the funding of the Midatech's R&D programs.



Source: Midatech Pharma Plc

Perhaps most importantly, Midatech US provides the company with an established sales channel in which to seamlessly integrate any products that are developed in-house. The ability to launch its own pipeline products is something that differentiates Midatech from other small-cap pharmaceutical companies. While most small biotech companies license products for milestones and royalties (typically 10-20% of net sales), by being able to sell a product on its own, Midatech stands to retain approximately 70% of net sales.

Financials and Capital Structure

As a foreign reporting entity, Midatech releases financial information semi-annually. For the first six months of 2017 the company reported £3.0 million in statutory revenue, compared to £2.6 million for the first six months of 2016. R&D expenditures were £2.1 million in the first half of 2017, which was approximately the same as in the first half of 2016. We anticipate R&D costs to increase in the second half of 2017 as the company begins clinical trials of MTD201 and MTX110. Distribution costs, sales and marketing expenses of £4.1 million and administrative costs of £6.9 million in the first half of 2017 were both approximately the same to their levels in the first half of 2016. Net loss for the first half of 2017 was £9.0 million, or 19 pence per share, compared to a loss of £6.2 million, or 25 pence per share, in the first half of 2016.

As of June 30, 2017, the company reported approximately £6.2 million in cash and cash equivalents. In September 2017, Midatech raised net proceeds of approximately £5.6 million from the sale of 12 million shares of stock on the London stock exchange at 50 pence per share. This should be sufficient to fund the company's operations for at least the next 12 months and see them through key upcoming inflection points, including data readouts for MTD201 and MTX110.

Following the most recent financing, Midatech has approximately 61.0 million shares of stock that trade on the London stock exchange. The company also has American Depository Receipts (ADRs) that trade on the Nasdaq Capital Market. Each ADR represents two of the company's ordinary shares. When factoring in the approximately 3.3 million stock options and 3.0 million warrants, the company has a fully diluted share count of approximately 67.3 million.

Risks to Consider

Clinical Risk: The largest risk to an investment in Midatech is that the product candidates have negative clinical data or emergent safety signals that preclude their further development. We believe this risk is somewhat mitigated for MTD201, as octreotide is already approved for the treatment of acromegaly and carcinoid syndrome in the form of an extended release polymer. MTX110 carries intermediate clinical risk, as the case report of a DIPG patient successfully treated through an expanded access protocol may not be replicated in a larger, controlled study. However, we believe there is minimal risk of safety issues with MTX110 as panobinostat is FDA approved for a different indication. Lastly, MTD119 is a very high-risk program since only one drug has been approved for the treatment of HCC since sorafenib was approved in 2007.

Commercialization Risk: Even if approved, both MTD201 and MTD119 would enter markets with large pharmaceutical companies commanding the vast majority of the market share. The company has established the U.S. sales infrastructure, which we believe is a nice differentiator for the company and will allow them to keep more of the upside on the commercial side, however that does not mean that the sales team will be successful in promoting the drugs should they gain approval or be successful in convincing physicians and payers to change prescribing habits. The company has guided for Midatech US to become breakeven in the first half of 2018, however there is no guarantee that group will become cash flow positive and may end up consuming valuable financial resources that could otherwise be spent on R&D.

Financing Risk: Midatech is currently unprofitable and the company just completed an offering that raised approximately £5.6, which we believe will be sufficient to get the company through important inflection points next year. However, the company will need to raise additional capital in order to continue financing the development of the company's lead product candidates and there is no guarantee that capital will be able to be raised at attractive terms or at all.

MANAGEMENT PROFILES

Jim Philips, MB, ChB – Chief Executive Officer

Dr. Phillips has a strong background in company leadership and business development, and is a physician by training. He founded Talisker Pharma in 2004, which was the first acquisition of EUSA Pharma in 2006. As President of Europe and Senior Vice President, Corporate Development of EUSA Pharma Inc., Dr. Phillips led the strategy resulting in the acquisition of OPI and its ultimate acquisition by Jazz Pharmaceuticals in 2012. Dr. Phillips is currently a Non-executive Director of Herantis Pharma plc (listed in Helsinki), Insense Ltd (a private spin-out from Unilever), and, until joining Midatech, was Chairman of Prosonix Limited, guiding its successful transformation into a respiratory focused business. Dr. Phillips initially held senior positions at Johnson & Johnson and Novartis Pharmaceuticals. At Novartis, he was in Clinical & Business Development and was a Board Director of the $1.3 billion Arthritis, Bone, Gastrointestinal, Haematology and Infectious Diseases business unit and a member of the company's Clinical Leadership Team. Dr. Phillips has been awarded "Best CEO-Pharmaceuticals Industry" for 2015.

Nick Robbins-Cherry – Chief Financial Officer

Mr. Robbins-Cherry is a Chartered Accountant and MBA with extensive commercial and finance experience gained in the life sciences, technology, and consulting sectors, including roles at CACI Limited, Johnson & Johnson, and ICI PLC. Mr. Robbins-Cherry has a strong track record in mergers and acquisitions and of managing complex multi-national businesses. He qualified with Coopers & Lybrand (now PricewaterhouseCoopers) and has a BSc in Pharmacology.

Craig Cook, MD – Chief Operating Officer/ Chief Medical Officer

Dr. Cook has more than 15 years of international experience in the pharma, biomedical, and high technology sectors including roles across a range of therapeutic areas, such as neurology, inflammatory, immunology, and endocrine, covering both drug development and medical affairs. He has established and led several healthcare initiatives, and held increasingly senior appointments at Johnson & Johnson, Eli Lilly, Novartis Pharma, and Serono Biotech. Dr. Cook is lead adviser for Ippon Capital SA's life sciences practice.

VALUATION

We are initiating coverage of Midatech Plc with a $6.50 valuation. Midatech has three platform technologies designed to allow for the delivery of existing pharmaceuticals to the “right place” at the “right time”. The Q-Sphera technology involves the consistent and precise encapsulation of active drug compounds within polymer microspheres. The microspheres are engineered to release the drug compound into the body in a controlled and consistent manner over an extended period of time. The Midacore gold nanoparticle (GNP) technology was developed for repurposing and improving key parameters of new and existing drugs, including how the drug is distributed in the body and targeting to specific tissues. The Nano Inclusion (NI) technology is utilized for potent small molecule chemotherapeutics that have minimal solubility at biological pH, which limits them to oral administration. When reformulated with the NI technology, the complexed molecules solubilize such that parenteral routes of administration can be employed. This enables local administration directly into the tumor. Midatech is further differentiated through its U.S. based sales force, which will allow the company to capture the full value of any approved products without the need to partner with a larger pharmaceutical company for sales in the U.S.

MTD201

MTD201 is a formulation of octreotide (Sandostatin® LAR®) that utilizes the company’s Q-Sphera technology to allow for once-monthly dosing. Sandostatin® LAR® is approved for the treatment of acromegaly and malignant carcinoid syndrome. Novartis, which sells Sandostatin® LAR®, is the market leader with $1.6 billion in revenues in 2016 (EvaluatePharma). Additional products sold for the treatment of acromegaly include Somatuline® (sold by Ipsen), which generated €538 million in 2016 revenues, and Somavert® (sold by Pfizer), which generated $232 million in 2016 revenue (EvaluatePharma). The approximately $2.2 billion market is relatively stable, however we believe that MTD201 could capture a reasonable (~5%-10%) portion of that market by offering physicians and patients a compelling alternative to Sandostatin® LAR® with some potential benefits, including a smaller needle and dosing volume, easier reconstitution, and favorable economics. Capturing just 5% of the market represents a potential $100 million opportunity.

MTX110

MTX110 is a novel formulation of panobinostat (Farydak®) being developed for the treatment of diffuse intrinsic pontine glioma (DIPG). It is formulated using the company’s NI technology, which allows for the local delivery of potent therapeutics through alterations in the compounds pharmaceutical properties to improve delivery, safety, and efficacy. We believe MTX110 is somewhat de-risked due to the use of an already approved drug and data showing MTX110 was well tolerated in patients treated through a compassionate use program. DIPG is a fatal disease with no current treatment options, thus development could be accelerated through the use of a surrogate endpoint in the upcoming clinical trial and accelerated approval should the drug be efficacious. Based on the number of patients who suffer from DIPG (approximately 1,000 worldwide) and the opportunity for orphan drug pricing (we model for ~$150,000/yr in the U.S.), we believe MTX110 could have peak revenues of approximately $50 million.

MTD119

MTD119 is the company’s lead development product utilizing the GNP technology and is being developed for the treatment of hepatocellular carcinoma (HCC). The drug includes a peptide that binds to a receptor overexpressed by HCC cells and a toxin (DM1) that is utilized in the approved antibody-drug conjugate Kadcyla® (the same toxin molecule with a different linker). While the HCC market is relatively small in the U.S. and E.U. (approximately 35,000 and 47,000 patients, respectively), it is a very big problem where the rates of hepatitis B and hepatitis C are high, such as in Asia (approximately 500,000 patients). There are only two drugs approved for front-line HCC, Nexavar® (sold by Bayer), which had revenue of $963 million in 2016, and Stivarga® (also sold by Bayer), which was recently approved by the FDA in April 2017 for HCC but had revenue of $304 million in 2016 from the treatment of colorectal cancer and GIST (EvaluatePharma). We believe a successful front-line treatment for HCC would likely expand the size of the market, which is already expected to exceed $1 billion in the next few years.

Valuation

We value Midatech using a probability adjusted discounted cash flow analysis that takes into account future revenues for MTD201, MTX110, MTD119, and the Midatech US products. For each of the products, we believe the

company will promote them in the U.S. through the use of the existing sales team and will partner for areas outside of the U.S and receive a royalty of 12%. We model for MTD201 and MTX110 to enter the U.S. market in 2020 and the E.U. market in 2021, with MTX119 entering both markets in 2024.

For MTD201, acromegaly is the value driver as only a very small fraction of the $1.6 billion in revenue for Sandostatin® LAR® was derived from malignant carcinoid syndrome. We estimate approximately 20,000 individuals in the U.S. and 47,000 individuals in the E.U. suffer from acromegaly. We model for MTD201 to be priced at a slight discount ($14,000/yr) to Sandostatin® LAR® ($16,000/yr) and to have peak revenues of approximately $50 million in the U.S. and €42 million in the E.U. We assign a 50% probability of approval, a 15% discount rate, and the current exchange rate to arrive at an NPV for MTD201 of £37 million.

For MTX110, we model for a 50% peak market penetration, as there are no other treatment options currently available for DIPG patients. Due to DIPG being an orphan disease, we believe that the drug will be priced at a premium at $150,000/yr (although this could end up being conservative), which leads to peak revenues in the U.S. of $25 million and in the E.U. of €10 million. Using a 50% probability of approval, a 15% discount rate, and the current exchange rate leads to a NPV for MTX110 of £23 million.

The largest potential opportunity for Midatech is MTD119 in liver cancer. While the markets in the U.S. and the E.U. are small (although we estimate they still represent $180 million and £150 million opportunities, respectively), China is by far the largest opportunity with 350,000 new cases of liver cancer every year (Chen *et al*., 2011). We believe an effective HCC drug could lead to peak revenues in China of $300 million. We assign a 25% probability of approval, given the fact that only 2 drugs have been approved for treating first-line primary liver cancer. Using a 15% discount rate and the current exchange rate leads to a NPV for MTD119 of £54 million.

We believe that revenues from Midatech US will grow at a good rate for the next few years mostly from a ramp up in sales of Zuplenz®, with revenues growing 30% and 20% in 2018 and 2019, respectively. We forecast for sales to then slowly rise to approximately £11 million annually. Using a 15% discount rate and the current exchange rate leads to a NPV for Midatech US of £60 million.

Combining the NPV for each of the company's programs, the current cash position, and an additional £15 million operating burn leads to a NPV of £170 million. Dividing this by the fully diluted share count of 67.3 million leads to a valuation of £2.39 per share. 1 ADR represents 2 shares of common stock, and using the current exchange rate (1 US dollar = 0.75 GBP) leads to a current valuation for the ADRs of approximately $6.50. Midatech is currently trading well below our valuation, which we believe may change quickly as investors become more familiar with the story and how rapidly the company's lead programs could enter the market.

PROJECTED FINANCIALS

Midatech Plc
Income Statement

Midatech Pharma Plc (in millions of £)	2016 A	1H A	2H E	2017 E	2018 E	2019 E
Midatech Pharma US	£5.6	£3.0	£3.5	£6.5	£8.5	£10.2
MTX110 - DIPG Glioma	£0.0	£0.0	£0.0	£0.0	£0.0	£0.0
MTD201 - Acromegaly and Carcinoma	£0.0	£0.0	£0.0	£0.0	£0.0	£0.0
MTD119 - Liver cancer	£0.0	£0.0	£0.0	£0.0	£0.0	£0.0
MTR103 - Glioblastoma	£0.0	£0.0	£0.0	£0.0	£0.0	£0.0
Grants & Collaborative Revenue	£1.3	£0.4	£0.5	£0.9	£0.5	£0.5
Total Revenues	**£6.9**	**£3.4**	**£4.0**	**£7.4**	**£9.0**	**£10.7**
Cost of Sales	£0.7	£0.3	£0.4	£0.7	£0.9	£1.3
Product Gross Margin	-	-	-			
Research & Development*	£6.7	£7.1	£4.4	£11.5	£12.0	£14.0
Distribution Costs, Sales and Marketing	£9.5	£4.1	£4.5	£8.6	£10.0	£11.0
Administrative Costs*	£9.2	£1.9	£2.0	£3.9	£4.0	£5.0
Impariment of Intangible Assets	£11.4	£0.0	£0.0	£0.0	£0.0	£0.0
Other Expenses	£0.0	£0.0	£0.0	£0.0	£0.0	£0.0
Operating Income	-£30.6	-£10.0	-£7.3	-£17.3	-£17.9	-£20.6
Operating Margin	-	-	-	-	-	-
Non-Operating Expenses (Net)	£1.26	£0.36	-£0.20	£0.16	£0.01	£0.01
Pre-Tax Income	-£29.3	-£9.7	-£7.5	-£17.2	-£17.9	-£20.6
Income Taxes Paid	-£9.2	-£0.6	-£0.7	-£1.3	-£1.0	-£1.0
Net Income	**-£20.2**	**-£9.0**	**-£6.8**	**-£15.8**	**-£16.9**	**-£19.6**
Net Margin	-	-	-	-	-	-
Exchange Gain/Losses	£3.23	-£0.15	-£0.10	-£0.25	£0.00	£0.00
Total Comprehensive Gain/Loss	**-£16.9**	**-£9.2**	**-£6.9**	**-£16.1**	**-£16.9**	**-£19.6**
Net Loss per Share	**-£0.56**	**-£0.19**	**-£0.13**	**-£0.31**	**-£0.24**	**-£0.24**
YOY Growth	-	-	-	-	-	-
Basic Shares Outstanding	36.1	48.7	54.0	51.3	70.0	80.0

Source: Zacks Investment Research, Inc. *David Bautz, PhD*

*Note: 1H17 R&D and Admin Costs changed to reflect reallocation of costs for future time periods

© Copyright 2017, Zacks Investment Research. All Rights Reserved.

HISTORICAL STOCK PRICE



© Copyright 2017, Zacks Investment Research. All Rights Reserved.

DISCLOSURES

The following disclosures relate to relationships between Zacks Small-Cap Research ("Zacks SCR"), a division of Zacks Investment Research ("ZIR"), and the issuers covered by the Zacks SCR Analysts in the Small-Cap Universe.

ANALYST DISCLOSURES

I, David Bautz, PhD, hereby certify that the view expressed in this research report accurately reflect my personal views about the subject securities and issuers. I also certify that no part of my compensation was, is, or will be, directly or indirectly, related to the recommendations or views expressed in this research report. I believe the information used for the creation of this report has been obtained from sources I considered to be reliable, but I can neither guarantee nor represent the completeness or accuracy of the information herewith. Such information and the opinions expressed are subject to change without notice.

INVESTMENT BANKING AND FEES FOR SERVICES

Zacks SCR does not provide investment banking services nor has it received compensation for investment banking services from the issuers of the securities covered in this report or article. Zacks SCR has received compensation from the issuer directly or from an investor relations consulting firm engaged by the issuer for providing non-investment banking services to this issuer and expects to receive additional compensation for such non-investment banking services provided to this issuer. The non-investment banking services provided to the issuer includes the preparation of this report, investment software, financial database analysis, organization of non-deal road shows, and attendance fees for conferences sponsored or co-sponsored by Zacks SCR. The fees for these services vary on a per-client basis and are subject to the number and types of services contracted. Fees typically range between ten thousand and fifty thousand dollars per annum. Details of fees paid by this issuer are available upon request.

POLICY DISCLOSURES

This report provides an objective valuation of the issuer today and expected valuations of the issuer at various future dates based on applying standard investment valuation methodologies to the revenue and EPS forecasts made by the SCR Analyst of the issuer's business.
SCR Analysts are restricted from holding or trading securities in the issuers that they cover. ZIR and Zacks SCR do not make a market in any security followed by SCR nor do they act as dealers in these securities. Each Zacks SCR Analyst has full discretion over the valuation of the issuer included in this report based on his or her own due diligence. SCR Analysts are paid based on the number of companies they cover. SCR Analyst compensation is not, was not, nor will be, directly or indirectly, related to the specific valuations or views expressed in any report or article.

ADDITIONAL INFORMATION

Additional information is available upon request. Zacks SCR reports and articles are based on data obtained from sources that it believes to be reliable, but are not guaranteed to be accurate nor do they purport to be complete. Because of individual financial or investment objectives and/or financial circumstances, this report or article should not be construed as advice designed to meet the particular investment needs of any investor. Investing involves risk. Any opinions expressed by Zacks SCR Analysts are subject to change without notice. Reports or articles or tweets are not to be construed as an offer or solicitation of an offer to buy or sell the securities herein mentioned.