Right Time, Right Place; Micro- & Nano-particles for Drug Delivery

Dr Paul Seaman, Head of Sustained Delivery

UK HealthTech Conference 2016, Cardiff
A Rapidly Growing International Specialty Pharmaceutical Company

**UK-based public company (plc)**
- c.110 employees across Europe & the US
- Diversified strategy and sources of revenue with innovative R&D pipeline
- Highly experienced pharma management team

**Established US Commercial Presence**
- Six marketed products: potential aggregate peak sales of $50 million
- Double-digit top-line growth expected over the next 12 months
- Expect lead product Q-Octreotide to be filed for marketing authorisation H1 2018

**Fully integrated R&D capabilities with two platform technologies**
- Glycan coated gold nanoparticles (GNP)
- CAD “printed” sustained-release microparticles (Q-Sphera)
- Drives a novel, lower risk development pipeline based on known therapeutic agents
- 1500m² cGMP manufacturing facility located in Bilbao, Northern Spain
2016 H1 Operational Highlights

• Excellent integration and sales performance from our newly acquired US commercial business
  • Six months to June $4.58m (£3.19m), growth of 104% vs. H1 2015

• Launch of our anti-nausea product Zuplenz® in the US
  • Approved for use in multiple indications in a $10bn US market

• Preparation for final development & commercialisation of Q-Octreotide
  • GMP production capability started in H1 – £0.7m investment in our Bilbao facility
  • PI study to start H1 2017 and filing for first marketing authorisations anticipated in 2018

• Product candidate testing in vivo for glioblastoma (GBM) and hepatocellular carcinoma (HCC)
  • Both programmes on track for initial product selection by end of 2016

• Dosing due to commence in first immunotherapy Phase I study for Type I Diabetes
  • Consortium includes Cardiff University and King’s College London

• Further positive progress seen in the OpsiSporin (MTD202) and MTX110/111 (DIPG) programmes
### Development Pipeline: 10 Programs

Development of multiple, high-value, targeted therapies for major diseases with unmet medical need.

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<tr>
<th>Cancer</th>
<th>RESEARCH</th>
<th>PRECLINICAL</th>
<th>PHASE I</th>
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| CNS/Ocular                      |          |             |         |          |           |
| OpsiSporin Uveitis MTD202       |          |             |         |          |           |

| Immunotherapy                   |          |             |         |          |           |
| Type 1 Diabetes Vaccine MTX102  |          |             |         |          |           |
| Immuno-Oncology Vaccine MTR     |          |             |         |          |           |
| Immuno-Oncology TAM MTR         |          |             |         |          |           |
• Partnered development programmes for high-value, targeted therapies for further indications
• Partnerships and collaborations with specialty and major pharmaceutical companies and universities
• Already revenue generating
Right Time

- APIs with short $t_{1/2}$ require regular injection
- Sustained delivery technologies greatly increase dosing intervals
  - hours to months
  - Improved patient experience, ↑ compliance and ↓ clinician time
  - ↑ efficacy/↓ adverse effects
- Increase in biologics driving drug delivery challenges
- Polymer microsphere systems established for >30 years
  - Safe, effective, well received by patients and healthcare professionals
- Existing manufacturing technologies have significant drawbacks
  - Complex/slow to administer, difficult to tune release profile, limited API compatibility, class 2 solvents, limited drug loading, polydisperse, wasteful (CoGs), require substantial investment
- **Midatech Pharma’s Q Sphera technology addresses these needs**
  - Long duration of action and tuneable release
  - Drug loading & size control enable reduced needle size/injection vol
  - Rapid resuspension and simple administration
  - Scalable, efficient and API-friendly manufacturing that uses only class 3 solvents
Q-Sphera – Midatech Pharma’s SR Technology Platform

**Proprietary Microsphere Platform**
Precision encapsulation platform enabling tuneable sustained drug release for chronic diseases:
- Emulsion-free synthesis with product monodispersity
- Precise control over particle size, morphology, release kinetics
- High drug loading, minimal burst release, essential to development of safe & effective therapies

**Controlled Release**
- Control release of API over period of 2 weeks-6 months following single injection
- API released in predictable and consistent fashion

**Printing** Drugs at Scale
- Innovative adaptation of industrial inkjet technology to enable “printing” of uniform drug-containing microparticles
- Printing 1,000,000 particles per second
- Lab scale - commercial

**Microparticles**
- Encapsulate drugs into micron sized particles - diameter =25μm
- Compatible with small molecules - peptides, oligonucleotides, proteins
- Tuneable using biodegradable polymers

**Advantages**
- Readily injected via minimally-invasive needles as fine as 30G
- Minimal pain
- Eye and other difficult/complex routes
- Process and cost efficiency
Q-Sphera – Midatech Pharma’s SR Technology Platform

Forming 30µm particles

@ ≈3 million per second
Q-Octreotide (MTD201)

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| 05 | Market worth over $2bn (Sandostatin LAR $1.6bn) |

**Advantages**
- Quicker and easier to reconstitute/administer
- Smaller needle
- Fewer injection failures
- Clinical visit time significantly reduced
- More cost efficient

**Positive pre-clinical data**
- Compares favourably with Sandostatin LAR
- Pharmacokinetic data correlates well with PD effects
- Injections well tolerated with no site reaction

**Steps to commercialisation**
- Pilot human pharmacokinetic study planned Q1 2017, followed by bioequivalence or therapeutic equivalence programme in H1-2 2017
- Marketing authorisation submission anticipated in the period Q4/17 - Q4/18

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Currently in final stages pre-clinical development
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Long-acting formulation of Octreotide acetate for chronic treatment of carcinoid (cancer) & acromegaly
- Manufactured in house
- Know-how and arising IP retained
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Peak market potential c.$100m pa
- Own sales targeted in the USA
- Centurion out-licence achieved for Turkish rights

Market worth over $2bn (Sandostatin LAR $1.6bn)
Q-Octreotide (MTD201)

- Positive non-clinical pharmacology
- PK compares favourably with Sandostatin LAR (SLAR)
- PK data correlates well with PD effects
- Low variability
- Injections well tolerated

- GMP Manufacturing
  - in house production
  - terminal sterilisation
  - Investing now for full commercialisation 2018
OpsiSporin (MTD202)

**Development pathway**
- IND enabling to commence Q1 2017
- Toxicology program will complete approx. Q4 2017
- Phase I Q4 2017/Q1 2018

**Successful PoC completed in several *in vivo* models**
- Clear dose response established in prophylactic model
- Efficacy established in therapeutic model
- PK supports 3-month duration of action

**Advantages**
- Product will be steroid and immunosuppressant sparing
- Delivered intravitreal ≈1000 fold lower doses than oral
- Currently no approved intravitreal cyclosporine or other immunosuppressant treatment option available

**01** Successful PoC completed in several *in vivo* models
- Clear dose response established in prophylactic model
- Efficacy established in therapeutic model
- PK supports 3-month duration of action

**02** OpsiSporin is injectable sustained release formulation of cyclosporine for treatment of non-infective uveitis

**03** Intravitreal injection via 27-30G needle directly to vitreous with minimal transfer to the bloodstream

**04** Orphan indication, application submitted Q3/16

**05** Uveitis rapidly growing ≈$1.3bn market, current treated by eyedrops, steroids and immuno-suppressives
OpsiSporin Efficacy

**Prophylactic Model**

**Therapeutic Model**

*Change from Baseline*

*Study Day*

**Dose response established**

**Efficacy established, similar to oral CsA reference**
Gold Nanoparticle (GNPs) Technology Platform

**TARGETING**
Multivalency - enables binding of several targeting and therapeutic agents to a single nanoparticle

**THERAPEUTICS**
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

**MOBILITY**
Small size ~1.5nm and defined charge allows transport to disease sites that are otherwise very difficult to reach

**COMPATIBILITY**
Ultra-small gold nanoparticles are bio-inert, non-toxic, non-immunogenic; do not generate immune-response

**SCALABILITY**
Internal GMP manufacturing facility

**EXCRETABILITY**
Drug conjugates eliminated via the kidneys and liver

Smallest particles in biomedical use: 10x-20x smaller than peers
Gold Nanoparticle (GNPs) Technology Platform

**GNP Core**
- **Charge**: sign, strength & density
- **Ligand shell**: depth
- **Ligand shell**: hydrophilicity
- **Gold core**: size and ligand density
- **Parameter combinations**

**HCC Product**
- **Liver targeting**
- **Tumour targeting**: GPC3-binding GNPs
- **Tumour targeting**: HepG2-binding GNPs

**GBM Product**
- **Tumour targeting**: Integrin binding – CTX GNPs
- **Tumour targeting**: Integrin binding – RGD GNPs
- **Tumour targeting**: GRP78 binding GNPs
- **Tumour targeting**: Glioma binding GNPs

**“Right place”**
- Biocompatibility - PK

**“Right effect”**
- Pharmacology - PD
Cellular Affinity For GNPs: Comparison Of Different Glycan Coated Particle Uptake in GBM and HCC

GNP design customised to maximise uptake for specific indication
GNP Targeting – Hepatocellular Carcinoma (HCC)

Target Specific Delivery

Cancer selectivity

In vitro evaluation of Glypican 3 Targeted GNPs

Cytotoxicity/Cytostasis

Uptake in HEPG2

Uptake HEPG2 (co-culture)

Uptake HUVEC (co-culture)

GNP construct
GNP-nonsense peptide
GNP-targeting peptide

In vitro evaluation of Glypican 3 Targeted GNPs

% Viability

0 50 100 150
Glioblastoma (GBM) (MTR103)

01 Combined targeting and therapeutic
- Development in conjunction with Dana Farber institute
- Initial candidate selection planned Q4 2016
- IND enabling to commence H1 2017
- Filing for marketing authorisation anticipated by 2020

02 Worldwide estimated 240,000 cases of brain and nervous system tumours per year
- GBM is most common, and most lethal, of these tumours

03 Survival typically 12 to 15 months
- Less than 5% surviving greater than five years

04 Orphan indication, application to be submitted

05 Systemic and intra-tumoural administration

• GNP’s targeted to bind tumour specific receptors on GBM cells; internalised GNP’s developed to release therapeutic payload intracellularly
• GNP design customised to maximise uptake for specific GBM indication

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• GNP’s targeted to bind tumour specific receptors on GBM cells; internalised GNP’s developed to release therapeutic payload intracellularly
• GNP design customised to maximise uptake for specific GBM indication
Liver Hepatocellular Carcinoma (HCC) (MTR104)

**Combined targeting and therapeutic**
- Initial candidate selection planned 2H 2016
- IND enabling to commence 1H 2017

**Sixth most frequent cancer globally and the second leading cause of cancer death**

**Surgical resection major treatment option**
- But only 10 – 20% can be removed completely

**Current chemotherapeutic options too toxic**
- Opportunity to reduce through targeting

**Orphan indication**

- Target receptors on HCC tumour cells
  GPC3 to bind and internalise GNPs
  where the therapeutic payload
  would be released
DIPG: Diffuse Interstitial Pontine Glioma (MTX110)

01 Midatech actively pursuing local delivery directly into the tumour through Convection Enhanced Delivery (CED) that delivers therapeutic constructs via a series of catheters fixed into the substance of the tumours

02 Ultra rare childhood brain tumour
- c1,000 cases / year worldwide
- Average survival, 7 months; universally fatal

03 Ultra-high unmet need, potential orphan indication

04 Compassionate use/named patient program: MTX110 (non-GNP nano-formulation solubilising)
- UK: two DIPG children treated monthly doses – encouraging safety and efficacy according to physician
- US: one DIPG patient received first dose MTX110

05 Research & Development next steps:
- Regulatory interactions through 2016 – high level of support for program by regulatory agencies
- Evaluating clinical trial for successful candidate constructs
Thank you

For further information: paul.seaman@midatechpharma.com or rob.rainey@midatechpharma.com