### Preliminary results of a first-in-human, first-in-class phase I study of MTL-CEBPA, a small activating RNA (saRNA) targeting the transcription factor C/EBP-α in patients with advanced liver cancer

**Background**
- Small cell lung cancer drugs designed to selectively upregulate therapeutic proteins by recruiting endogenous transcription complexes to target genes, leading to increased expression of naturally processed mRNA
- Transcription factor CEBPα (C/EBPα/enhancer-binding protein alpha) is a leucine zipper protein which acts as a master regulator of liver homeostasis and multiple oncogenic processes including cell cycle control, proliferation and angiogenesis
- MTL-CEBPA comprises a double stranded RNA payload formulated inside a SMARTicles™ liposomal nanoparticle to specifically target the CEBPα gene and has shown to improve liver function and inhibit HCC tumour growth in preclinical models (Reebye et al, Hepatology, 2018; Vouill et al, Molecular Therapy, 2017; Reebye et al, Oncogene, 2018)
- MTL-CEBPA is the first saRNA and the first drug targeting C/EBPα

**Methods**
- 4 week cycle (3 weeks dosing + 1 week rest)
- MTL-CEBPA administered by intravenous infusion over 60 minutes
- Pre-medication may be administered to prevent infusion reactions
- AE, PK and PD assessed
- Radiological response determined by RECIST 1.1 every 8 weeks (2 cycles)
- All data are preliminary and based on a cut-off of March 31, 2018

**Safety**
- No patients experienced maximum grades 4 and 5 AEs
- Most common AEs: Grade 1/2 hyperbilirubinaemia (75%) and hypophosphataemia (11%)
- One patient with secondary liver cancer experienced a Grade 3 dose limiting toxicity at 70 mg/m²

**Pharmacokinetics**
- Mean terminal elimination half-life 36h (range 19-56h) with dose proportional Cmax and AUC versus baseline
- Mean follow up period of 3.5 months

**Pharmacodynamics**
- Significant increased expression of CEBPA mRNA in WBC supports target engagement
- Significant and repeated increase in CEBPA on baseline consistent with C/EBPα-dependent granulopoiesis

**Pharmacodynamics**
- 78 year old female, hepatitis B related cirrhosis, prior trans-arterial chemoembolisation, radiofrequency ablation and liver resection, surgical and experimental FGFR4 antibody
- Radiological outcome: partial response (-42%) at Week 8, confirmed at Week 16 (-63%)
- Correlation with a drastic and rapid increase in CEBPA mRNA with significant increase in expression up to 75% at 12 weeks
- Maintained response (~75%) after 20 cycles (1.5 year)

**Key Inclusion Criteria**
- Unresectable, histologically confirmed HCC or secondary liver cancer
- HCC only recruited from cohort 3b prior sorafenib
- Child-Pugh class A or B with no non-cirrhotic ascites
- EOGD status 0-3
- At least one measurable liver lesion (≥1.0 cm)

**Baseline Demographics and Characteristics**

<table>
<thead>
<tr>
<th>Characteristic, No. (%)</th>
<th>Total (n=10)</th>
<th>CEC (n=5)</th>
<th>CEBPA (n=5)</th>
</tr>
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<tbody>
<tr>
<td>Median age, years (range)</td>
<td>64 [27-81]</td>
<td>65 [37-81]</td>
<td>63 [27-81]</td>
</tr>
<tr>
<td>Gender: Male</td>
<td>7 (45)</td>
<td>3 (60)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Mean follow up period of 3.5 months</td>
<td>14 (7)</td>
<td>7 (14)</td>
<td>7 (14)</td>
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**Response Biomarkers: mRNA expression in WBC**

**Discussion**
- 3+3 ascending doses with MTL-CEBPA weekly is well tolerated.
- Alternative dosing schedule now enrolling based on preclinical data suggesting increased up regulation of CEBPA and greater anti-tumour efficacy
- PK for QW dosing described well by linear and dose proportional two-compartment model
- Target engagement supported by increased CEBPA gene expression in WBC driving enhanced granulopoiesis

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