Pancreatic cancer study Atu027-I-02
Interim analysis

1 June 2015
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Atu027 background

Atu027 is Silence’s most advanced RNA interference drug:

- Gene silencing mechanism engineered to target production of the protein PKN3, combined with our proprietary lipoplex delivery system

- PKN3 discovered in-house as a key factor in metastasis. Extremely robust patent position in the role of PKN3 in cancer

- Atu027 shown in extensive preclinical studies to have anti-metastatic effect by targeting systemic vasculature. Complements therapies targeting primary tumours

- Phase 1 safety study in patients with advanced solid tumours completed 2013, good safety and tolerability profile:
  
  Results presented at ASCO 2013
  Data published in Journal of Clinical Oncology

Progressed to Phase 2a open-label safety study in 23 patients with incurable pancreatic cancer, completed recruitment in July 2014

Atu027 – mode of action

- **PKN3 silencing** in vascular endothelium increases systemic barrier function of vessels
- **Anti-metastatic therapeutic hypothesis** based on the reduction of intravasation and extravasation of cancer cells

Reduced lung metastatic burden in **rodent model**

**Therapeutic target knock down in NHP:**

- **PKN3 mRNA** knock down (lung)
- **PKN3 protein** knock down (lung)
Why pancreatic cancer?

High unmet medical need

- Pancreatic cancer is the fifth most common cause of death by cancer in EU and the seventh worldwide
- 338,000 new cases diagnosed every year worldwide
- Five year survival rate of 3% - improved little since 1970s*

Pre-clinical research in pancreatic cancer

Pre-clinical proof of concept

- **Atu027** tested in combination with standard of care, gemcitabine, in a mouse model of pancreatic cancer:
  - Impaired invasive growth and lymph node metastasis
  - Prolonged overall survival

Combination approach tackles both primary tumour and metastases
Purpose of the phase 2a study

To evaluate:

1. **Atu027 safety** in combination with gemcitabine in patients with incurable metastatic and locally advanced pancreatic carcinoma
2. The **efficacy** of Atu027 in combination with gemcitabine

Study Population

- **Main Inclusion criteria:**
  - 18 – 84 years
  - Non curable locally advanced or metastatic pancreatic carcinoma stage III/IV, indicated for gemcitabine treatment
  - Life expectancy 3 months or more
  - Reasonable liver and kidney function

- **Main exclusion criteria**
  - Cardiac disease
  - Poorly controlled diabetes
  - Poorly controlled hypertension
  - Anticancer chemotherapy, immunotherapy or radiotherapy during the study or before
Atu027-I-02: Trial design

Multi-Center Study in Germany

**Phase 2a – Incurable Pancreatic Cancer** (loco-regional + metastatic)

**Arm 1**

- 3 patients
- 28-d combination cycle

**Arm 2**

- 23 patients
- 28-d combination cycle

**Lead in Safety Cohort**
Refractory cancers

**Gemcitabine**
1000 mg/m²

**Atu027**
0.253 mg/kg

28-d combination cycle

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Endpoints

• Primary endpoints:
  — Safety
    • Adverse events
    • Vital signs
    • Body weight
    • 12-lead electrocardiogram (ECG; including QTc)
    • Clinical laboratory parameters including haematology, clinical chemistry, and urinalysis

• Secondary endpoints:
  — Efficacy
    • RECIST objective response rate
    • Progression Free Survival (PFS)
    • Overall Survival (OS)
  — Quality of Life
Homogenous trial population

Subject baseline data and disposition (safety analysis set)

<table>
<thead>
<tr>
<th></th>
<th>All tumours</th>
<th>Metastatic only*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arm 1 11 patients</td>
<td>Arm 2 12 patients</td>
</tr>
<tr>
<td>Male</td>
<td>36.4%</td>
<td>41.7%</td>
</tr>
<tr>
<td>Female</td>
<td>63.6%</td>
<td>58.3%</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>61.6</td>
<td>67.6</td>
</tr>
<tr>
<td>Mean</td>
<td>64 (43/74)</td>
<td>71 (44/80)</td>
</tr>
<tr>
<td>Median (min/max)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>67.73</td>
<td>67.51</td>
</tr>
</tbody>
</table>

* Due to significant differences in tumour behaviour and based on the assumed mode of action of Atu027, a separate efficacy analysis of all metastatic cancer patients was performed.
**Primary endpoint: Safety**

Percentage of subjects with an adverse event reported in more than 2 subjects (safety analysis set)

<table>
<thead>
<tr>
<th>AE (PT)</th>
<th>All tumours</th>
<th>Expected incidence with gemcitabine alone as monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arm 1 11 patients</td>
<td>Arm 2 12 patients</td>
</tr>
<tr>
<td>Nausea</td>
<td>45%</td>
<td>58.3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27.3%</td>
<td>41.7%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>45.5%</td>
<td>41.7%</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>27.3%</td>
<td>41.7%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18.2%</td>
<td>25.0%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0.0%</td>
<td>25.0%</td>
</tr>
<tr>
<td>Malignant neoplasm progression</td>
<td>27.3%</td>
<td>16.7%</td>
</tr>
<tr>
<td>TOTAL number of subjects reporting AE *</td>
<td>100%</td>
<td>91.7%</td>
</tr>
</tbody>
</table>

* 11 subjects reported AE in both arms

\(^1\) In combination with either paclitaxel or carboplatin

**AE consistent with side effects recorded for gemcitabine**

Additional toxicity unlikely to be caused by Atu027 incorporation to gemcitabine regime
Primary endpoint: Safety

Percentage of subjects with a clinical laboratory parameter reported as adverse event in more than 2 subjects (safety analysis set)

<table>
<thead>
<tr>
<th>AE (PT)</th>
<th>All tumours</th>
<th>Arm 1 (11 patients)</th>
<th>Arm 2 (12 patients)</th>
<th>Expected incidence with gemcitabine alone as monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td></td>
<td>27.3%</td>
<td>50.0%</td>
<td>68%</td>
</tr>
<tr>
<td>C-reactive protein increased</td>
<td></td>
<td>18.2%</td>
<td>25.0%</td>
<td></td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td></td>
<td>27.3%</td>
<td>33.3%</td>
<td>63%</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td></td>
<td>27.3%</td>
<td>66.7%</td>
<td>24%</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td></td>
<td>18.2%</td>
<td>25.0%</td>
<td>30%&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td></td>
<td>18.2%</td>
<td>25.0%</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>1</sup> in combination with cisplatin

AE consistent with side effects recorded for gemcitabine
Additional toxicity unlikely to be caused by Atu027 incorporation to gemcitabine regime
No other significant safety signals

Other safety endpoints (safety analysis set)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All tumours</th>
<th>Arm 1 11 patients</th>
<th>Arm 2 12 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in body weight in kg (baseline to EoT/PT)</td>
<td></td>
<td>-1.75</td>
<td>-2.44</td>
</tr>
<tr>
<td>ECG changes to Clinically Significant</td>
<td></td>
<td>0</td>
<td>1 (previously abnormal, not clinically significant)</td>
</tr>
<tr>
<td>Vital signs:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Atu027 was well tolerated:
No significant safety signals related to differential Atu027 administration
Secondary endpoint: Efficacy

Progression Free Survival (safety analysis set)

<table>
<thead>
<tr>
<th>All tumours</th>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11 patients</td>
<td>12 patients</td>
</tr>
<tr>
<td>Mean PFS (months)</td>
<td>3.23</td>
<td>4.15</td>
</tr>
<tr>
<td>SE</td>
<td>1.02</td>
<td>0.73</td>
</tr>
<tr>
<td>Median (months)</td>
<td>1.81</td>
<td>5.33</td>
</tr>
<tr>
<td>Min/Max</td>
<td>0.39/9.76</td>
<td>1.02/7.26</td>
</tr>
<tr>
<td>P value (Chi-square)</td>
<td>0.3985</td>
<td></td>
</tr>
</tbody>
</table>

Subjects without progression of disease (or death) are censored at date of FU-1 visit. In case of premature termination without a FU-1 visit they are censored at the documented date of last contact with the subject.
Efficacy: post-hoc analysis

Separate post-hoc analysis of the efficacy parameters for **all subjects** and subjects with metastatic cancer only:

**Rationale:**

- The mechanism of action of Atu027 suggests it works by impairing metastatic disease

**Exclusions:**

- In each arm there were 2 subjects with locally advanced cancer. In each arm 1 of these subjects withdrew consent before the End of Treatment (EoT), making PFS assessment impossible. These subjects are censored for Kaplan-Meier curves.
Progression Free Survival – metastatic only

Progression Free Survival (safety analysis set)

<table>
<thead>
<tr>
<th>Metastatic tumours</th>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9 patients</td>
<td>10 patients</td>
</tr>
<tr>
<td>Mean PFS (months)</td>
<td>1.96</td>
<td>3.99</td>
</tr>
<tr>
<td>SE</td>
<td>0.60</td>
<td>0.82</td>
</tr>
<tr>
<td>Median (months)</td>
<td>1.61</td>
<td>2.89</td>
</tr>
<tr>
<td>Min/Max</td>
<td>0.39/5.29</td>
<td>1.02/7.26</td>
</tr>
<tr>
<td><strong>P value (Chi-square)</strong></td>
<td>0.0247</td>
<td></td>
</tr>
</tbody>
</table>

Subjects without progression of disease (or death) are censored at date of FU-1 visit. In case of premature termination without a FU-1 visit they are censored at the documented date of last contact with the subject.
Measuring patient benefit

Absolute change from baseline for quality of life according to European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire

Patients in Arm 2 reported superior quality of life (Metastatic cohort only)
Phase 2a conclusions

- Primary endpoint of safety achieved:
  - **No safety issues** detected for the combination of Atu027 with gemcitabine
  - Atu027 shown to be **well tolerated**. Quality of life data suggest an improvement in the higher dose arm (arm 2)
  - Results add to existent safety and tolerability clinical dataset (Atu027 now tested in 60 patients in oncology)

- Promising signal in efficacy (secondary endpoint):
  - **Dose-dependent effect in PFS** shown between the two arms. Subjects exposed to a 33% higher total dose of Atu027 presented longer duration of PFS than patients in the lower exposure arm
  - **Statistically significant** difference in PFS observed between arms for the metastatic cohort
Acknowledgements

Atu027 Phase 2a Investigators

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• Prof. Martin Wolf. Klinikum Kassel.
• Prof. Thomas Seufferlein. Universitätsklinikum Ulm.
• Dr. Karin Link. Klinikum Nürnberg Nord.

Monitoring, data management, statistical analysis support

• FGK Clinical Research GmbH. Munich.
COMMERCIAL OPPORTUNITY
## Approved treatment options

### Limited treatment options for incurable pancreatic carcinoma patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mode of action</th>
<th>Approval date</th>
<th>Benefit over Gemzar (median PFS, Phase III results)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gemzar</strong></td>
<td>Cytotoxic (nucleoside analogue)</td>
<td>1996</td>
<td>N/A</td>
</tr>
<tr>
<td>(Gemcitabine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Folfirinox</strong></td>
<td>Combination of 4 cytotoxic agents</td>
<td>2011</td>
<td>ΔPFS: 3.1 months</td>
</tr>
<tr>
<td><strong>Abraxane</strong></td>
<td>Anti-mitotic (β-tubulin targeting)</td>
<td>2013</td>
<td>ΔPFS (in combination with Gemzar): 2.8 months</td>
</tr>
<tr>
<td><strong>Tarceva</strong></td>
<td>EGFR inhibitor</td>
<td>2005</td>
<td>ΔPFS (in combination with Gemzar): 11 days</td>
</tr>
<tr>
<td><strong>Atu027</strong></td>
<td>Anti-metastatic (PKN3 targeting)</td>
<td>--</td>
<td>TBD. Positive signal in Phase 2a</td>
</tr>
</tbody>
</table>

- Poor results with current standard of care: marginal benefit in survival and highly toxic
- Atu027 has a good opportunity of becoming a targeted anti-metastatic therapy in pancreatic cancer
Continuation of pancreatic programme

Next steps:

• **CMC** upscaling activities initiated

• Phase 2a one year **follow-up data** due early 2016

• **Optimal dosing schedule** for PKN3 knock-down to be established preclinically

• **Larger Phase 2** trial to be planned in next 18 months
  - Initial focus on metastatic pancreatic cancer
  - Efficacy as primary endpoint

Further preclinical testing (NHP) → Regulator input and application for *Orphan status* and *Breakthrough* → Phase 2 study in metastatic pancreatic cancer → Phase 3 subject to positive Phase 2 results
## Continuation of pancreatic programme

**Discussions with regulators and statisticians planned:**

### Potential scenarios *

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Studies (approx. number of patients)</th>
<th>Investment estimate †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orphan drug status only granted</td>
<td>Phase 2 (150)</td>
<td>c. £6m</td>
</tr>
<tr>
<td></td>
<td>Phase 3 (300)</td>
<td>c. £12m</td>
</tr>
<tr>
<td>Breakthrough designation and orphan status granted</td>
<td>Phase 2/3 (300)</td>
<td>c. £12m</td>
</tr>
</tbody>
</table>

* Assuming orphan drug status will be granted  
† Subject to statistical and regulatory input

### Beyond clinical development in pancreatic cancer:

- Atu027 applications not limited to pancreatic cancer
- Clinical need for anti-metastatic drugs across solid tumours