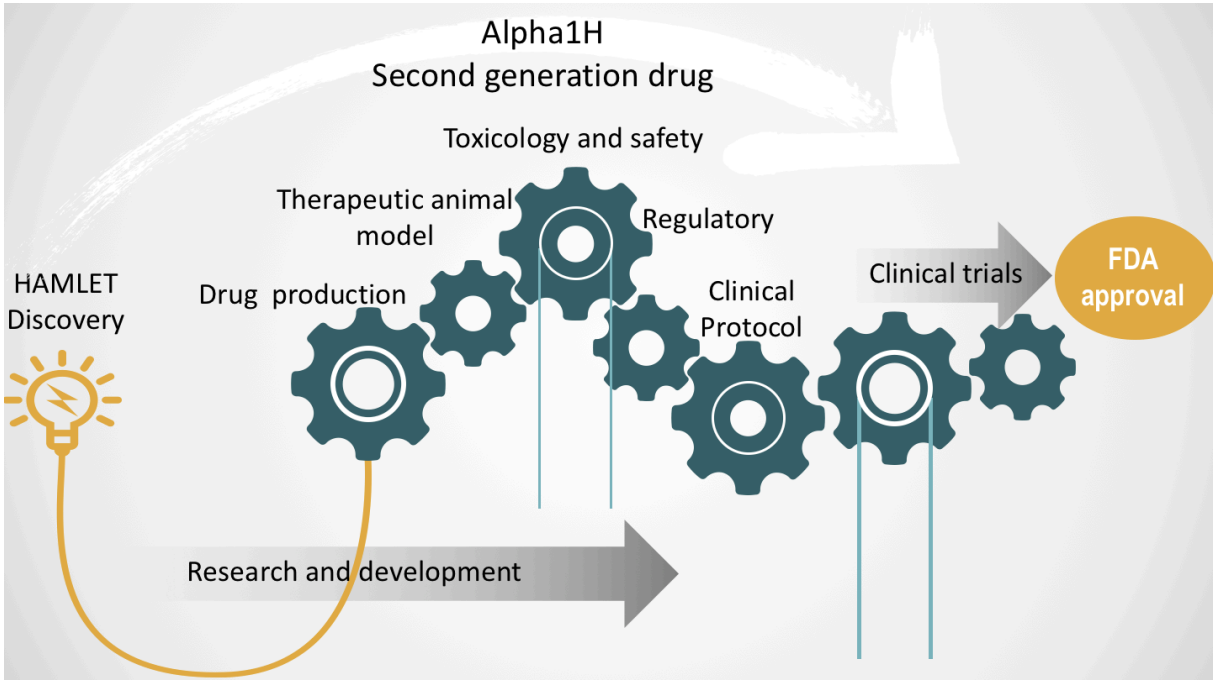
HAMLET PHARMA NEWSLETTER

THE PHASE I/II CLINICAL TRIAL IN PATIENTS WITH BLADDER CANCER

The discovery of HAMLET defines a new class of cancer drugs with broad effects against cancers of different origin and a high degree of selectivity. Our aim is to prove the efficacy of HAMLET therapy and to develop drugs that kill tumour cells with greater precision than most current drugs.

Hamlet Pharma Ltd. is making great progress and preparations to start the first clinical trial in patients with bladder cancer are rapidly moving forward. In this newsletter, we briefly summarise recent advances and present an overview of the clinical study protocol that will be used. Drug development often takes many years, due to complex development and approval processes. Based on our extensive prior experience, the drug candidate Alpha1H has passed a number of important milestones in a relatively short time and with moderate cost.

Development plan, milestones



We have rapidly and successfully developed important technologies that now are available for the start of the clinical trial. These include

1. – *The second generation drug candidate Alpha1H*

Detailed molecular studies have allowed us to make a map of the protein and to identify domains responsible for the effect on tumor cells. Based on the science, we have developed a new synthetic drug candidate Alpha1H, which is the business end of HAMLET and kills tumor cells with similar efficacy.

The peptide can be synthesized in large amounts and activated by the addition of the lipid, just like HAMLET. We can now guarantee the supply of material needed to initiate placebo-controlled clinical trials.

2. - *GMP production*

Clinical studies require large quantities of the drug candidate, produced in accordance with GMP, as well as documentation, according to the guidelines of the European authorities and the American FDA. The first manufacturing batch, also called "engineering batch", has been analysed with positive results.

Hamlet Pharma has successfully established large-scale production of the active compound Alpha1H with full GMP standards. The peptide-based technology has added precision, reduced the complexity of the GMP approval process and lowered production costs. In addition, the patent life of the peptide complexes lasts until 2031. The peptide production technology will also make it possible for the company to explore additional clinical indications and out-licensing of selected therapeutic areas.

3. *Therapeutic effects in animal models*

In animal studies local HAMLET treatment limited the progression of brain tumors, colon cancer and bladder cancer, suggesting that HAMLET could be used to prevent tumor development in genetically susceptible individuals. Using the engineering batch of the synthetic Alpha1H complex, we have also shown that Alpha1H reproduces the therapeutic activity of HAMLET, against bladder cancer, in a murine model.

4. Toxicology and safety studies

A central goal of cancer therapy is to achieve selectivity for the tumor and minimal toxicity for healthy tissues. Tissue toxicity and side effects are still the norm, however, and even though new, targeted therapies act with greater precision, the notion of tumor specific mechanisms of cell death is justly regarded with scepticism.

Yet, α1H and HAMLET have not shown toxicity for healthy cells or tissues, in animal models or clinical studies. We are performing toxicity studies to exclude any unwanted effects of Alpha1H.

5. Regulatory process

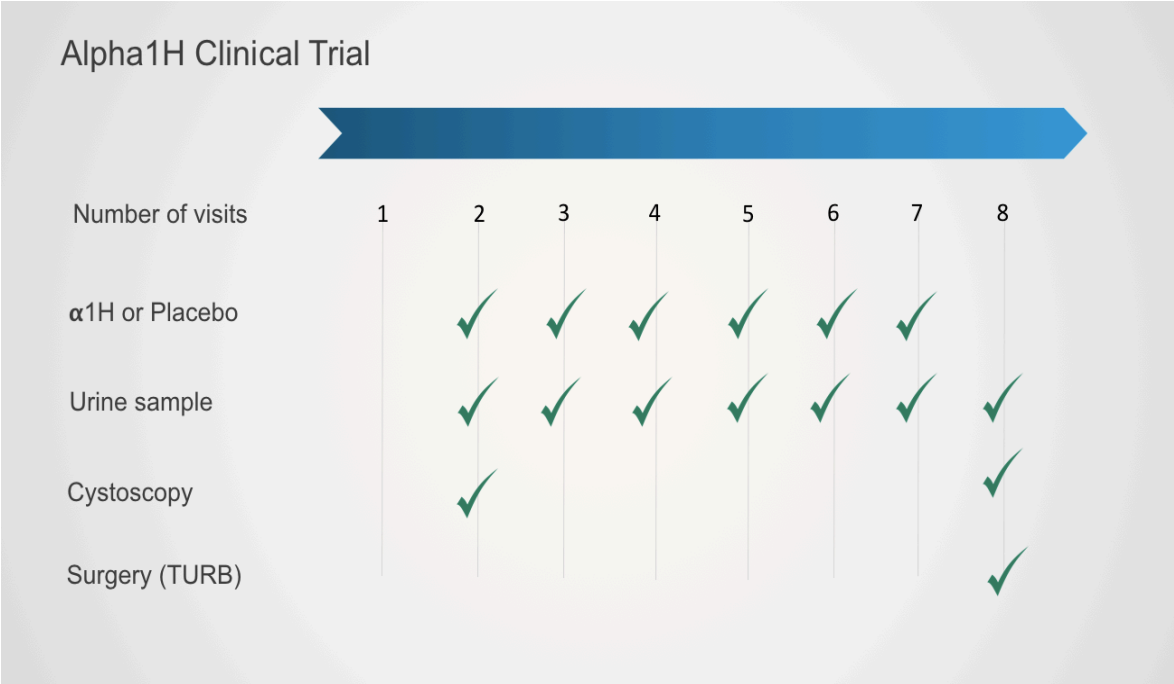
We have drafted key documents needed to initiate clinical trials, including the Investigator's brochure, Clinical trial protocol and Ethical application forms.

6. Clinical trial protocol

The safety and efficacy of Hamlet Pharma's drug candidate α1H will be investigated in patients with bladder cancer. Clinical studies have shown that HAMLET is active against **bladder cancer**, as local HAMLET injections

caused shedding of tumour cells into the urine. HAMLET altered the morphologic appearance of the tumour and triggered cell death in tumour tissue. The healthy adjacent tissue was left untouched, and the patients did not report any toxic side effects.

We will conduct a single centre, randomised, double-blind trial in patients with non-muscle invasive bladder cancer. The trial will compare Alpha1H to placebo and will determine the safety and efficacy of Alpha1H by measuring outcomes such as tumour size and cell death. The trial will enrol patients consecutively until the designated number is reached.



- Clinical trial organization

The clinical trial will be conducted at a leading European centre for bladder cancer studies, in compliance with European regulatory requirements. The investigator has prepared the clinical trial protocol jointly with Hamlet Pharma, as well as the study design and documentation for the ethics application. The subjects will receive six intra-vesical instillations of α1H or placebo.

The trial will be monitored by a well-respected Contract Research Organization (CRO), in accordance with applicable guidelines. The CRO will

ensure that the study meets both European and US FDA quality standards. In addition, they will be responsible for Data Management, Statistics and Pharmacovigilance.

7. Evaluation

The study is designed to collect data on safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of Alpha1H and to evaluate the efficacy of Alpha1H as a cancer drug. The study will use cell shedding after instillations of Alpha1H as a biomarker of cancer cells death. The change in tumour size will be an important measure of effect, together with molecular end points.

Why clinical trials matter?

The strategic goal of Hamlet Pharma is to develop novel cancer treatments for patients who currently lack therapeutic options. Conducting clinical trials is crucial to reach primary goals such as evaluating the therapeutic window for HAMLET in bladder cancer. We also aim to gain new insights that facilitate the drug development for Alpha1H and the diversification of our activities to include other indications.