

Oncology program

Confirmation of the clinical effects observed with CER227185 – Major achievements in the development of CER233790 and new tumour reversion promoters

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Cerep has pursued the development of drug candidates for the treatment of cancer based on the principle of tumour reversion.

A Phase I/II clinical trial aiming to validate the concept of tumour reversion in man with the first clinical compound, CER227185 has been continued. The new data reinforce the promising results previously published.

In parallel, Cerep has developed a new compound, CER233790, exhibiting strong anti-tumour activity. Studies have demonstrated that CER233790 presents an improved safety profile as compared to CER227185. CER233790 is today ready to enter the pre-IND regulatory phase.

In addition, based on the same principle, the company has discovered third-generation anti-tumour agents which are 50 to 100 fold more potent than CER233790 in *in vitro* models.

■ Confirmation of the encouraging clinical results for CER227185

CER227185 is the first candidate taken by Cerep to a Phase I/II clinical trial. The compound was administered by oral route to refractory or relapsed acute myeloblastic leukaemia (AML) patients. This trial allowed determining the maximal tolerated dose of CER227185, 400 mg/day. In this trial 3 out the 10 first patients (two of these three receiving 400 mg/day) showed remarkable survival time (from 250 days to nearly one year compared to a median survival time of 90 days for such AML patients). Moreover a decrease in the rate of circulating tumour cells has been observed in certain patients.

In an extension of this first study, 6 additional patients were treated at the maximal tolerated dose, and two of them have shown a survival time of more than 275 days, re-enforcing the trends observed in the first 10 patients.

The new results obtained thus confirm the validity and therapeutic promise of the tumour reversion approach undertaken by Cerep.

Cerep scientists and clinicians believe that adverse effects of CER227185 are not linked to the anti-tumoral mechanism of action, but rather to its interaction with unrelated targets present in the central nervous system. Cerep has therefore decided not to pursue the development of CER227185 beyond the current Phase I/II study but to focus its efforts on the development of compounds with reduced off-target effects, in particular CER233790 which does not interact with targets responsible for CER227185 side effects.

■ CER233790, the new clinical candidate, has shown efficacy in human tumours, as well as an improved safety profile. It causes a cell cycle arrest and a decrease of protein synthesis in tumour cells.

CER233790 is a metabolite of CER227185 which presents remarkable properties. This compound retains the marked anti-tumour activity of CER227185, and good oral bioavailability, while demonstrating a reduced binding to the targets associated with the secondary effects of CER227185. This allows the use of CER233790 at optimal doses.

CER233790 has demonstrated a remarkable anti-tumour effect on cell lines from both solid tumours (breast, colon, ovary, prostate, skin, brain, pancreas), and haematological cells of human origin at doses compatible with its clinical use.

Furthermore Cerep has shown that CER233790, in addition to its effects on TCTP, the key target in the tumour reversion process, causes a blockade in cell cycle progression at phase G1. CER233790 also causes an arrest of protein synthesis in treated tumour cells.

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- **CER 233790 displays targeted effect on tumour cells from patients without affecting normal cells**

The effect of CER233790 was tested, in collaboration with the scientists at Hôpital Saint-Louis (Paris-France), on blood cells taken directly from patients with different myeloblastic diseases: AML, chronic myeloblastic leukaemia, polycytemia vera. Cells were maintained in *ex vivo* culture under conditions allowing differentiating normal from malignant cells. In all cases treatment of patient cells with CER233790 leads to a very significant decrease of the viability of tumour cells while minimally or not affecting the viability of normal cells.

These remarkable results suggest that treatment of patients with CER233790 could lead to an objective clinical response, with limited adverse effects.

- **Development of third-generation compounds**

In parallel to the development of CER233790 the chemists of Cerep have developed a new series of compounds with significantly improved anti-tumour activity, evaluated *in vitro*. These new compounds have 50 to 100 fold better activity and possess the physico-chemical and biological properties compatible with their use by oral administration. The detailed characterization in animal models of the most promising of these compounds will be initiated.

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Cerep's mission is to provide pharmaceutical companies with high quality services in drug discovery and drug development as well as drug candidates at different preclinical and clinical stages. Cerep provides solutions allowing faster and cost effective drug discovery by identifying at early stages the most promising drug candidates as well as eliminating those compounds likely to fail in development. Cerep's integrated platform encompasses a complete range of technologies including chemistry, biology, and informatics.

Cerep's technologies benefit to more than 360 pharmaceutical and biotechnological companies worldwide including most of the top pharmaceutical firms. Cerep's drug pipeline includes collaborative drug candidates developed with Sanofi-Aventis and Bristol-Myers Squibb, as well as products discovered on its own (including one compound in phase I/II clinical trial in the field of cancer). Cerep's development strategy aims at self-financing its research.

Statements included in this press release which are not historical in nature are intended to be, and are hereby identified as, "forward-looking statements" for purposes of the safe harbor provided by Section 21E of the Securities Exchange Act of 1934, as amended by the Private Securities Litigation Reform Act of 1995. Forward-looking statements may be identified by words including "anticipates", "believes", "intends", "estimates", "expects" and similar expressions. The company cautions readers that forward-looking statements, including without limitation those relating to the company's future operations and business prospects, are subject to certain risks and uncertainties that could cause actual results to differ materially from those indicated in the forward-looking statements. Factors that may affect future operations and business prospects include, but are not limited to, clinical and scientific results and developments concerning corporate collaborations and the company's proprietary rights and other factors described in the company's Document de référence.