HYBRIGENICS

Press Release

Encouraging preliminary results of the Phase II clinical study of inecalcitol in Chronic Myeloid Leukemia

Paris, France, 09 February 2017 – Hybrigenics (ALHYG), a bio-pharmaceutical company listed on the Alternext market of Euronext Paris, with a focus on research and development of new treatments of proliferative diseases, today gives an update on the Phase II clinical study of inecalcitol in chronic myeloid leukemia (CML) administered in addition to imatinib, the reference inhibitor of BCR-ABL kinase used as standard of care for CML.

In CML, the quantitative parameter predicting efficacy of BCR-ABL kinase inhibitors is the reduction in expression of the BCR-ABL fusion gene causative in CML cases: a 3 log decrease (1,000-fold) in BCR-ABL is called a major molecular response (MMR) and a 4.5 log decrease (31,623-fold) a deep molecular response (DMR). Between the MMR and DMR levels, the disease is considered to be under control with continuous daily administration. With levels sustained in DMR, the minimal residual CML disease is sufficiently low that treatment cessation can be considered and functional cure achieved in some patients.

The ongoing, open-label Phase II study evaluates the efficacy of oral inecalcitol added to oral imatinib in CML patients who, after at least two years of treatment with imatinib alone, have achieved MMR but not DMR, with the objective to reach DMR within one year of treatment. Twenty-one patients have been enrolled to date: twelve remain under treatment and nine have completed one year of treatment. At this intermediate stage of study, 43% of the patients (6 out of 14) have shown further decrease in BCR-ABL from MMR at three months, and after one year of treatment, 33% (3 out of 9) have demonstrated reduction in BCR-ABL beyond DMR, i.e. undetectable biomarker traces.

These results can be compared with two recently published independent reports which demonstrate a simple 7.5% yearly increase in the percentage of patients reaching DMR under imatinib alone (Hochhaus *et al.*, Leukemia, March 2016; Cortes *et al.*, Journal of Clinical Oncology, July 2016).

Based on these intermediate results and a very low study drop-out rate, the sample size of this pilot study has been reduced to 42 patients, with a target completion in H2 2018. Hybrigenics' Clinical Advisory Board has reviewed these preliminary observations and made suggestions to widen the scope of the potential clinical use of inecalcitol in CML.

"*Inecalcitol should show similar effects in addition not only to imatinib, but also to second-generation BCR-ABL kinase inhibitors, since we have demonstrated in Chronic Myeloid Leukemia stem cells isolated from patients that the same synergy exists between inecalcitol and all BCR-ABL kinase inhibitors*," said Prof. A. Turhan, Head of the Division of Hematology, Paris-Sud Kremlin-Bicetre University Hospital.

"*In Chronic Myeloid Leukemia, some Deep Molecular Responders relapse after having stopped BCR-ABL kinase inhibitors. They have to resume treatment indefinitely and often the BCR-ABL kinase inhibitors alone are not expected to permit further attempts at treatment free remission. Adding inecalcitol in this clinical setting may ensure full efficacy and increase the chance for durable cure,"* said Prof. M. Mauro, Leader, Myeloproliferative Neoplasms Program, Memorial Sloan Kettering Cancer Center, New York.

"*These preliminary results are encouraging but remain to be confirmed on the total number of patients. They also give ideas on how to exploit the full potential of inecalcitol in Chronic Myeloid Leukemia,*" said Jean-François Dufour-Lamartinie, Hybrigenics' Chief Medical Officer.

About Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML), also known as chronic myelogenous leukemia, is the least frequent of the three main adult leukemias. In 2016 in the United States, 8,220 new cases have been diagnosed, a total of at least 36,700 patients were living with the disease and about 1,070 have died from CML; the 5-year survival rate is 63% (LLS Cancer Facts and Figures, 2016). In France, the number of new cases diagnosed each year is estimated at 810 (Francim, 2013). In Europe, the incidence is 1.02 patient per year per 100,000 inhabitants (EuTOS, 2014). CML has orphan disease regulatory status in Europe, Japan and the United States.

CML is a type of cancer that starts in the bone marrow, invades the blood and then other parts of the body such as the spleen. CML evolves slowly at the beginning and, without treatment, ends by deteriorating into acute ("blast") phases similar to Acute Myeloid Leukemia, causing deadly anemia, coagulation impairment or lack of defense against infections. CML is characterized by the over-production of all types of white blood cells (except lymphocytes) originating from a single stem cell, which escapes proper normal regulations.

In all CML patients, the loss of cell control results from the same "exchange" of "bits" of chromosomes ("translocation" between chromosomes number 9 and 22), which gives rise to the abnormal fusion gene called BCR-ABL. The product of this gene, the Bcr-Abl protein is a hyper-functional kinase which continuously stimulates cell proliferation. The inhibitors of the Bcr-Abl kinase such as imatinib, dasatinib, nilotinib or ponatinib, are used to treat CML patients and the BCR-ABL gene transcripts are well-established biomarkers of the blood concentration of residual CML cells.

About Hybrigenics

Hybrigenics (www.hybrigenics.com) is a bio-pharmaceutical group listed (ALHYG) on the Alternext market of Euronext Paris, focusing its internal R&D programs on innovative targets and therapies for the treatment of proliferative diseases.
Hybrigenics' development program is based on inecalcitol, a vitamin D receptor agonist active by oral administration. Inecalcitol has been tested in chronic lymphocytic leukemia patients, an indication for which inecalcitol has received orphan drug status in Europe and the United States. Two clinical Phase II studies of inecalcitol are currently ongoing in chronic myeloid leukemia and acute myeloid leukemia. Oral inecalcitol has shown excellent tolerance and strong presumption of efficacy for the first-line treatment of metastatic castrate-resistant prostate cancer in combination with Taxotere®, which is the current gold-standard chemotherapeutic treatment for this indication.
Hybrigenics' research program is exploring the role of enzymes called Ubiquitin-Specific Proteases (USP) in the balance between degradation and recycling of proteins called onco-proteins due to their involvement in various cancers. Hybrigenics is evaluating the interest of inhibitors of USP as anti-cancer drug candidates. Hybrigenics has collaborated with Servier on one particular USP in oncology. In this R&D program, two steps have been reached and additional milestones may be achieved until registration of a potential drug.
Hybrigenics Corp., based in Cambridge, Mass., is the American subsidiary of Hybrigenics.

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