Hybrigenics full year 2017 results and update on the clinical studies of inecalcitol

- Completion of the Phase II clinical study in Chronic Myeloid Leukemia
- 87 out of 110 patients enrolled in the Phase II clinical study in Acute Myeloid Leukemia
- Cash position of EUR 7.0 million as of December 31st, 2017

Paris, France, on April 26th, 2018 – Hybrigenics (ALHYG), a bio-pharmaceutical company listed on the Euronext Growth market of Euronext Paris, with a focus on research and development of new anticancer treatments, today announces its consolidated results for the full year ended December 31st, 2017 and gives an update on the clinical studies of inecalcitol.

2017 full year results

Hybrigenics' 2017 annual results take into account the MBO and sales of its controlling stakes in Hybrigenics Services, its subsidiary dedicated to proteomic scientific services (cf. press release of March 13th, 2017), and of Helixio, its business unit dedicated to genomic services (cf. press release of February 19th, 2018), which constitute the discontinued operations. The clinical development of inecalcitol and the drug discovery research on inhibitors of Ubiquitin-Specific Proteases (USPs) represent Hybrigenics' retained and ongoing activities.

IFRS (EUR million)	**2017**	**2016[a]**	**Change**
Turnover	0	1.5	-100%
Other operating revenues[b]	1.9	1.1	+73%
Total operating revenues	**1.9**	**2.6**	**-27%**
Total operating costs	(9.3)	(6.6)	+41%
Operating loss	**(7.4)**	**(4.0)**	**+85%**
Net loss from discontinued activities	(0.8)	(0.2)	+300%
Result from the sale of discontinued activities	0.1	(1.1)	+109%
Net loss	**(8.0)**	**(5.3)**	**+51%**
Cash position of retained activities (at year end)	**7.0**	**8.5**	**-18%**

[a]restated from the impacts of the sales of Hybrigenics Services and Helixio
[b]revenues from subleases, services to subleasers and current year research tax credit

Hybrigenics' 2016 turnover from retained and ongoing Pharma R&D activities comes from the partnership with Servier in the field of USPs: EUR 1.5 million payment was received as a milestone payment in this drug discovery research collaboration (cf. press release of October 10th, 2016). The next milestone has not been reached yet, which explains that no turnover has been booked in 2017. Other operating revenues have increased from EUR 1.1 to 1.9 million. In total, Hybrigenics' operating revenues have decreased from EUR 2.6 to 1.9 million.

Operating costs have increased from EUR 6.6 to 9.3 million due to the sustained pace of patient enrolment in the clinical Phase II study of inecalcitol in acute myeloid leukemia in France and in the United States, and to the preparation of its extension to Belgium, Spain and Germany. Operating loss has increased from EUR 4.0 to 7.4 million and net loss from EUR 5.3 to 8.0 million.

Hybrigenics has raised EUR 6.8 million with the success of a rights issue in July 2017. As of December 31st, 2017, the cash position of Hybrigenics' retained activities was EUR 7.0 *vs.* EUR 8.5 million one year ago.

Results of the Phase II clinical trial in chronic myeloid leukemia (CML)

Oral Inecalcitol has been studied in France only in an open-label Phase II trial in addition to oral imatinib, the reference inhibitor of BCR-ABL kinase used as standard of care. CML is caused by the same BCR-ABL fusion gene in all CML patients. The quantitative parameter predicting efficacy is the reduction in the expression of this BCR-ABL fusion gene: 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 of BCR-ABL kinase inhibitors. With levels maintained in DMR, the minimal residual CML disease is sufficiently low that treatment cessation can be considered and functional cure achieved in some patients.

The clinical study of inecalcitol has focused on CML patients who, after at least two years of treatment by imatinib alone, have achieved MMR but not DMR, with the objective to reach DMR within one year of treatment combining inecalcitol and imatinib. Twenty-two patients have been enrolled in total; twenty patients have completed one full year of treatment. Eight patients (40%) have shown further decrease in BCR-ABL from MMR and, at the end of treatment, four patients (20%) have demonstrated reduction in BCR-ABL beyond DMR, *i.e.* undetectable biomarker traces. By comparison, the increase in DMR during one year of treatment with imatinib alone has consistently been reported as 7.5% in two independent studies (Hochhaus *et al.*, Leukemia, 2016; Cortes *et al.*, Journal of Clinical Oncology, 2016).

Inecalcitol has shown its ability to decrease residual CML disease beyond what can usually be achieved by imatinib alone, the first-generation reference BCR-ABL kinase inhibitor. Knowing what inecalcitol can add to the activity of second- or third-generation BCR-ABL kinase inhibitors such as dasatinib, nilotinib, bosutinib or ponatinib would be useful to assess its full potential in this therapeutic indication. Due to prioritization of resources allocation, the decision on the design and the launch of the next clinical trial of inecalcitol in CML will be made after the results of the clinical study in acute myeloid leukemia updated below.

Update on the Phase II clinical trial in acute myeloid leukemia (AML)

Oral inecalcitol is currently being tested in an international double-blind placebo-controlled Phase II study in AML patients unfit for standard chemotherapy, in combination with intravenous monthly cycles of decitabine. A total of 87 patients have been enrolled so far, mainly in France and in the United States since the last quarter of 2016. The first patient in Belgium has been enrolled in 2017 and the first patient in Spain in 2018. The primary endpoint is overall survival and the objective to enroll a total of 110 patients should be reached before the end of this year, with final results expected in 2019.

The synergy between decitabine, an hypomethylating agent, and inecalcitol, a vitamin D receptor agonist, was discovered in 2014 by a team of researchers led by Pr. O. Hermine, Head of Hematology, Necker Hospital, Paris, France. Hypomethylating agents "unmask" the gene coding for vitamin D receptors, by reducing the methylation of its promoter region; as a consequence, more vitamin D receptors are expressed and available to be activated by inecalcitol (cf. Hybrigenics' press release of June 20th, 2014). A patent application had been filed at the time and according to a material transfer agreement having enabled the testing of inecalcitol, Hybrigenics has recently enacted its intellectual property rights on the patent family resulting from this application. If granted, these patents could protect the therapeutic use of inecalcitol in combination with hypomethylating agents, such as decitabine or azacytidine, in Europe, North America and Japan until June 18th, 2034.

"Following its strategic refocusing on Pharma R&D, Hybrigenics' accounts of retained and ongoing activities are much simpler. Operating expenses reflect the intensity of investments mostly in two Phase II clinical trials of inecalcitol, which have proven productive with the completion of the study in Chronic Myeloid Leukemia and the high pace of patient enrolment in the study in Acute Myeloid Leukemia, which is given the highest priority," **said Remi Delansorne, Hybrigenics' CEO.**

About Hybrigenics

Hybrigenics (www.hybrigenics.com) is a bio-pharmaceutical group listed (ALHYG) on the Euronext Growth 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 metastastic 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 milestones have been reached and additional milestones may be achieved until registration of a potential drug.

Hybrigenics Pharma Inc., based in Cambridge, Mass., is the U.S. subsidiary of Hybrigenics.

Hybrigenics is listed on the Alternext market of Euronext Paris

ISIN: FR0004153930
Ticker: ALHYG

Hybrigenics
Rémi Delansorne
CEO
Tel.: +33 (0)1 58 10 38 00
investors@hybrigenics.com

NewCap
Financial communication
Julien Perez / Pierre Laurent
Tel.: +33 (0)1 44 71 94 94
hybrigenics@newcap.eu