EDISON

Hybrigenics

Outlook

Inecalcitol shows promise in CML, R&D refocus

Pharma & biotech

Hybrigenics' main focus is the development of inecalcitol as a niche treatment for leukaemia. In February it presented encouraging initial results for inecalcitol in combination with oral imatinib in chronic myeloid leukaemia (CML), with 43% of patients responding in a Phase II study that will complete in H218. A Phase II trial in acute myeloid leukaemia (AML) is ongoing with data expected in H119. Inecalcitol is Phase III-ready for chronic lymphocytic leukaemia (CLL) where it slowed progression in half of patients. The company has sold the proteomic services division and refocused on biopharma R&D. Our valuation is €141m; net cash at end 2016 was €8.5m.

Year end	Revenue (€m)	PBT* (€m)	EPS* (c)	DPS (c)	P/E (x)	Yield (%)
12/15	2.2	(4.5)	(13.2)	0.0	N/A	N/A
12/16	3.6	(3.9)	(10.8)	0.0	N/A	N/A
12/17e	3.7	(4.9)	(13.8)	0.0	N/A	N/A
12/18e	5.6	(3.6)	(9.9)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding intangible amortisation, exceptional items and share-based payments. Accounts have been restated to reflect the sale of 75.8% of Hybrigenics Services.

Inecalcitol's strategic positioning in oncology

Interim data for inecalcitol in combination with oral imatinib in CML showed that 43% of patients achieved a major molecular response (MMR). Moreover, after one year 33% of patients achieved a deep molecular response (DMR). A DMR could lead to functional cures and potential cessation of treatment, avoiding side effects and reducing the economic burden of tyrosine kinase inhibitors (TKIs). A Phase II study in AML is ongoing, after preclinical studies showed increased survival in animal models of AML. Lastly, inecalcitol also has potential in CLL where it slowed progression in 52% of patients. It is Phase III-ready, awaiting funding.

Refocus on biopharma R&D

Hybrigenics has sold its controlling stake in the proteomics services division to management for €796k in total. It continues the discovery and development of new inhibitors of deubiquitinating enzymes (DUBs), particularly the subset known as ubiquitin-specific proteases (USP). Hybrigenics has a solid patent portfolio and protection until 2032. The oncology deal with Servier continues, with up to €12m in potential milestone payments until registration.

Valuation: DCF of €141m or €3.9 per share

Our DCF valuation is €141m or €3.9 per share, from €146m or €4.1 per share. The key change to our numbers relates to inecalcitol in CML, where we have increased the probability of success to 40% from 30% due to positive interim data; and to CLL, where we have reduced the probability of success to 20% from 30% as we await guidance on the development path. We have also updated our model for the FY16 net cash position of €8.5m.

12 May 2017

Price	**€0.81**
Market cap	**€29m**

Net cash (€m) at 31 December 2016	8.5
Shares in issue	35.8m
Free float	87%
Code	ALHYG
Primary exchange	Alternext
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	2.5	(15.6)	(6.9)
Rel (local)	(2.8)	(24.3)	(25.1)
52-week high/low		€1.10	€0.71

Business description

Hybrigenics is a French biotech company. It is conducting Phase II studies on lead drug inecalcitol in orphan adult leukaemias: chronic myeloid leukaemia and acute myeloid leukaemia.

Next events

Orphan designation in CML in EU & US	2017
CML Phase II completion	H218
AML Phase II data	H119

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Edison profile page

Hybrigenics is a research client of Edison Investment Research Limited

Investment summary

Company description: Focus on adult leukaemias

Hybrigenics is a French biotech company formed from a spinout from Institut Pasteur. Its main activity is developing vitamin D analogue inecalcitol as a treatment for adult leukaemias, in particular chronic lymphocytic leukaemia (CLL), chronic myeloid leukaemia (CML) and acute myeloid leukaemia (AML); and for other solid tumours. In addition, it has a drug discovery collaboration with Servier based on the ubiquitin-specific proteases class and focused on oncology in pre-clinical development. Hybrigenics' services activity now only comprises the Helixio division providing specialised genomics services for life sciences researchers from academia or pharmaceutical, cosmetic and agrochemical industries. Hybrigenics is listed on Alternext and entered the CAC PME mid-cap index in April 2014.

Valuation: DCF valuation of €141m

Our risk-adjusted DCF valuation is €141m or €3.9 per share, a slight decrease from €146.1m or €4.1 per share due to changes in the probability of success of inecalcitol in CML and CLL. We have increased the probability of success in CML from 30% to 40% on the back of the positive interim data. Development of inecalcitol in CLL is currently paused, despite its potential, because Hybrigenics requires funding or a partner to move development forward in this indication. Therefore, until we have further updates on the development plans, we are reducing the probability of success from 30% to 20%. For AML we assume in Europe that the company retains rights, but in the US we assume for both AML and CML that commercialisation is partnered with a 25% royalty rate. Inecalcitol in CLL forms the highest proportion of our sum-of-the-parts valuation at €78m, while CML is €74m and AML accounts for €43m. After the management buyout of Hybrigenics Services, which represented c 80% of the services division revenues, we have removed the proteomics services subsidiary from our valuation and include a forecast of the retained genomics services division, Helixio and Pharma R&D. We include our forecast of the milestone payments from the collaboration with Servier. Preclinical projects and inecalcitol's value in prostate cancer are excluded.

Financials: FY16 results and rebased forecasts

FY16 revenue grew 66% to €3.6m, mainly due to a €1.5m milestone payment from Servier and restated to reflect the sale of the controlling stake in Hybrigenics Services. Helixio's FY16 sales increased by 70% from €0.6m to €1m. For FY17 we estimate group revenues broadly unchanged at €3.7m without any Servier milestone payment. This includes our estimated 40% increase in the reshaped service revenues to €1.4m. FY16 operating costs were €7.1m vs €6.1m in FY15 and we forecast an increase in FY17 costs to €8m to cover the Phase II trials. Hybrigenics' net cash position was €8.5m at end December 2016. We estimate the company is funded into 2018.

Sensitivities: Biotech clinical development

The key sensitivity is the rate of progress in developing inecalcitol in haematological cancers with the usual clinical, regulatory and financial challenges of biotech development. Hybrigenics has sufficient funds to carry out the Phase II trials in AML and CML, but would be reliant on further financing or a partnership to progress into further clinical trials in any or all three haematological indications, and potentially prostate cancer. Our assumptions are based on the company self-funding approval studies of inecalcitol in leukaemia. The sale of the proteomic services division significantly reduces the diversification of its business model and increases the risk profile of the company.

Inecalcitol: Strategic positioning in leukaemias

Hybrigenics has adopted a development strategy with vitamin D3 derivative inecalcitol, initially focusing on adult haematological cancers, based on the anti-proliferative potency and safety profile demonstrated in preclinical studies as well as clinical studies in CLL and prostate cancer. The investment case rests on inecalcitol's potential to enhance rather than to replace approved therapies, particularly in view of the significantly weakened general health of older leukaemia patients who are unable to tolerate therapies with harmful side effects. Inecalcitol has orphan drug designation for CLL and AML in the US and Europe and the company is pursuing orphan status in CML based on the promising interim data recently published. Our peak sales estimate is US$735m across the three indications. Hybrigenics' proteomics services subsidiary has been subject to a management buyout and the company offers genomics services through Helixio. With two ongoing clinical trials, the company is focused on biopharmaceutical R&D; in particular on DUB inhibitors and its ongoing collaboration with Servier that could yield up to €12m in further development and regulatory milestone payments until drug registration.

Inecalcitol: Combining potency with safety

Vitamin D plays a role in many cellular mechanisms including cell proliferation and apoptosis as well as inflammation and immunomodulation. Inecalcitol demonstrates up to 15 times the anti-proliferative potency of calcitriol, the active form of vitamin D, on cancer cells *in vitro*. At the same time, inecalcitol has an excellent safety profile and its chemical structure leads to over 100-fold lower calcium toxicity than calcitriol, a major dose-limiting characteristic of other vitamin D3 derivatives.

Exhibit 1: Clinical pipeline

Indication	Status	Setting	Notes
CML	Phase II ongoing	+ imatinib/stable chronic phase	The efficacy endpoint is the proportion of responders, defined as patients achieving a deep molecular response (DMR) within 12 months of inecalcitol treatment. At interim, 43% of patients who had been on treatment for three months showed improvements to baseline MMR (major molecular response). Additionally 33% of patients who had completed one year in the study achieved a DMR. Target enrolment 42 patients in France.
AML	Phase II ongoing	Newly diagnosed frail or elderly patients ineligible for standard chemo + decitabine	Primary endpoint is overall survival. Designated as an orphan drug in the US and EU. Target enrolment 110 patients in US and France
CLL	Phase II completed	Monotherapy/untreated/ high risk of progression	21 untreated patients dosed with 2mg oral inecalcitol for at least five months; disease progression was halted in 11 patients (52% of cases). Designated as an orphan drug in the EU and US. Next stage Phase III disease progression study.
Castration-resistant prostate cancer (CRPC)	Phase IIa completed	+ docetaxel/all patients	Dose-finding and safety study established daily 4mg oral dose – 40 out of 47 of patients exhibited an 85% reduction in PSA levels within three months, compared to a 65% reduction in PSA levels on docetaxel alone (in external registration study). Phase IIb proof-of-concept next development stage.

Source: Hybrigenics, Edison Investment Research

Hybrigenics is developing inecalcitol in three haematological cancers: CLL, CML and AML. Exhibit 2 shows the main grouping of haematological cancers divided into the lymphoid and myeloid leukaemias.

Exhibit 2: Overview of leukaemia

	Chronic (slow growing)	Acute (fast progression)
Myeloid	**Chronic myeloid leukaemia (CML)** Slow growing, abnormal production of myeloid cells About 10-15% of all newly diagnosed leukaemia **Treatment:** generally by targeted therapy, ie Gleevec	**Acute myeloid leukaemia (AML)** Group of fast growing diseases, abnormal production of myeloid cells About 30-40% of all newly diagnosed leukaemia **Treatment:** generally chemotherapy, sometimes stem cell transplant
Lymphocytic	**Chronic lymphocytic leukaemia (CLL)** Slow growing, abnormal production of lymphocytes About 30% of all newly diagnosed leukaemia **Treatment:** often contains fludarabine; mAbs including Rituxan	**Acute lymphocytic leukaemia (ALL)** Fast growing immature lymphocytes 10-15% of all newly diagnosed leukaemia **Treatment:** chemotherapy, Gleevec (Ph+ only), transplant

Source: Edison Investment Research

Promising initial data in CML: 43% of patients respond

Inecalcitol is undergoing a Phase II study in patients with chronic myeloid leukaemia (CML). This is an open-label study that plans to enrol 42 patients in France. The study assesses oral inecalcitol administered in combination with oral imatinib in patients with incomplete molecular response after at least two years on imatinib. At February 2017 the trial had enrolled 21 patients and will complete in H218, according to Hybrigenics. The CML programme is built on the back of preclinical data in which inecalcitol in combination with imatinib demonstrated synergistic effects in experiments *in vitro* by inhibiting the proliferation of CML stem cells, which are involved in relapse. The trial aims to replicate this effect and prolong remission or achieve a functional cure.

The primary endpoint is the proportion of responders measured by the reduction in the expression of the BCR-ABL oncogene. Efficacy in CML can be measured as haematological response, which measures white cells count; cytogenetic response, which tests Philadelphia chromosome in the marrow; and molecular response, which measures expression of BCL-ACR by PCR in circulating blood cells.

Exhibit 3: Definitions of response

Type	Type of response
Haematological response	■ Partial response (PHR): reduction in white cells, but not to normal levels. ■ Complete response (CHR): white cells count at or below approximately 12,000 white cells/µl.
Molecular response	■ Major molecular response (MMR): 3 log reduction in the amount of BCR-ABL protein. BCR-ABL less than or equal to 0.1% in International Scale (IS). ■ Deep molecular response (DMR): MR4 (4 log reduction, BCR-ABL ≤ 0.01%); MR4.5 (4.5 log or BCR-ABL≤0.0032%) or MR5 (5 log or BCR-ABL ≤0.001%).*
Cytogenetic response	■ Cytogenetic response (CR or CyR): any reduction in Ph+ chromosome reading. ■ Major cytogenetic response (MCR or MCyR): 0%-35% of Ph+ cells in the marrow ■ Complete cytogenetic response (CCR or CCyR): no Ph+ cells can be measured.

Source: Edison Investment Research; *Cross et al. *Leukemia*. 2012

In February 2017 Hybrigenics presented the first clinical data from the study. At the interim analysis, inecalcitol plus imatinib showed a further decrease from MMR in six of 14 patients at three months (43%). Additionally, three of nine patients (33%) who have completed one year in the study had a DMR.

Comparison with other clinical studies

The Phase III DASISION study one-year MR4.5 was 5% for dasatinib and 3% for imatinib. The two-year MR4.5 rate was 19% for dasatinib and 8% for imatinib.

Exhibit 4: MR4.5 DASISION study

Arm	1 year	2 years	3 years	4 years	5 years
Dasatinib 100mg once daily (n=259)	5%	19%	24%	34%	42%
Imatinib 400mg once daily (n=260)	3%	8%	13%	23%	33%

Source: Edison Investment Research, Cortes et al. *Journal of Clinical Oncology*. 2016

The ENESTnd Phase III clinical trial comparing two doses of nilotinib vs imatinib in newly diagnosed CML patients showed that at one year 7% and 11% of nilotinib and only 1% of imatinib patients achieved an MR4.5 response. At two years up to 25% of patients on nilotinib achieved an MR4.5, while 9% of patients in the imatinib arm achieved an MR4.5.

Exhibit 5: MR4.5 ENESTnd

Arm	1 year	2 years	3 years	4 years	5 years
Nilotinib 300 mg twice daily (n=282)	11%	25%	32%	40%	54%
Nilotinib 400 mg twice daily (n=281)	7%	19%	28%	37%	52%
Imatinib 400 mg once daily (n=283)	1%	9%	15%	23%	31%

Source: Edison Investment Research, Hochhaus et al. *Leukemia* 2016

In the absence of a comparator that shows the MR4.5 at different points in time with and without imatinib; and with the limited data disclosed, it is difficult to discern what proportion of the effect is attributed to inecalcitol. Cross-trial comparisons are difficult, but if we assume that patients have been on imatinib for at least two years and, that inecalcitol is added for one year, which is a total of three years, then a 33% MR4.5 is better than 15% at three years in the ENESTnd imatinib arm, and comparable to 32% in the nilotinib arm. Likewise, these data compare better than 24% and 13% in the dasatinib and imatinib arms in the DASISION study, respectively. Therefore, we believe that these preliminary data could be considered positive, while we await full one-year data.

Exhibit 6: Comparison

Arm	3 years	4 years	5 years
Imatinib DASISION	**13%**	23%	33%
Imatinib ENESTnd	**15%**	23%	31%
Inecalcitol + imatinib	**33%**	**(imatinib at least 2 years + inecalcitol 1 year)**	

Source: Edison Investment Research

Value proposition: Increase response to stop treatment

The first-line treatment for CML is tyrosine-kinase inhibitors (TKIs). Most patients on TKIs achieve a lasting molecular response. Moreover, with the advent of second-generation TKIs, such as nilotinib (Tasigna, Novartis) and dasatinib (Sprycel, BMS), more patients can achieve further responses, raising the expectations that survival improves, and second-generation TKIs may potentially achieve a functional cure for the disease. Recent data show that patients who achieve DMRs can safely cease their therapy without relapsing, which is called treatment-free remission (TFR). Even patients who do relapse can still be responsive to other TKIs. Around 40% of patients who stop treatment after achieving stable DMR remain in TFR.

Guidelines from the US National Comprehensive Cancer Network (NCCN) and the European LeukemiaNet (ELN) recommend TKI treatment indefinitely in all patients who respond to treatment. However, long-term treatment with TKIs has been associated with side effects and loss of quality of life. Furthermore, these products have an economic burden. Gleevec's list price is $120k per year per patient in the US; Sprycel and Tasigna cost about the same. Gleevec's US patent has expired and generic imatinibs from Teva and Sun Pharma have reached the market, although no information on pricing is available. In Europe, most TKIs cost around $30k per year per patient. Therefore, achieving lasting deep molecular responses that could take the patient off treatment would represent an innovative approach to improve patients' quality of life and reduce costs. Inecalcitol could fit in this strategy and become an adjunct to other therapies, rather than directly competing with them. We believe that the Phase II initial data show the potential impact of inecalcitol on the CML treatment paradigm due to its benign safety profile and potential to further improve molecular responses leading to discontinuation of treatment and functional cures.

Based on official epidemiology sources, such as the US National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results (SEER) programme and the European Treatment and Outcomes Study (EUTOS) for CML, we estimate c 14,250 new CML patients per year in the EU and US. We forecast EU/US peak sales for inecalcitol of $257m in CML. The company plans to apply for orphan drug status in the EU and US based on these initial data.

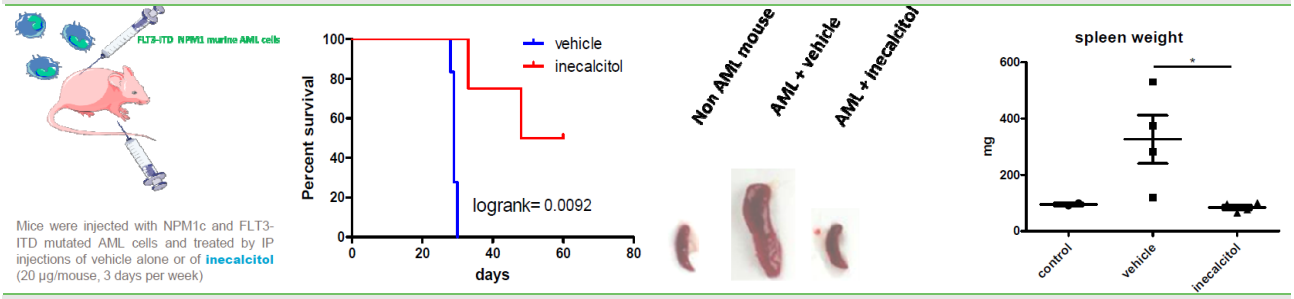
First patients enrolled in Phase II AML study

During H216 Hybrigenics started enrolment in a Phase II study of inecalcitol in patients with acute myeloid leukaemia (AML). The study is a double-blind, placebo-controlled trial that will recruit 110 patients (55 in the US and 55 in France) over 65 years' old and unfit for chemotherapy. Daily doses of oral inecalcitol (4mg) or placebo will be administered to patients who can only receive monthly

cycles of decitabine infusions. The primary endpoint is overall survival and secondary endpoints are response rate and tolerance. The company guides for data read out in H119. Inecalcitol has orphan drug status in Europe and the US.

Preclinical data were presented at the 12th International Congress on Targeted Anticancer Therapies in 2014. Inecalcitol prolonged survival and reduced splenomegaly (increase in spleen size and weight) in FLT3 animal models of AML as shown in Exhibit 7.

Exhibit 7: Preclinical AML data



Source: Hybrigenics

Moreover, *in vitro* data presented at the American Association for Cancer Research (AACR) annual meeting 2017 in cell lines of AML and multiple myeloma (MM) showed that inecalcitol is able to turn these into less invasive and more functional cells, in addition to its anti-proliferative properties.

Based on updated epidemiology data, we estimate c 40,000 new AML patients in EU and US and peak sales of $119m.

There are a range of treatments in the late stages of development shown in Exhibit 8, including those targeting FLT3, eg midostaurin and quizartinib, in Phase III trials being targeted for treatment of older patients ineligible for chemotherapy.

Exhibit 8: Competing therapies for AML

Product/company	Setting	Status	Notes
Inecalcitol/ Hybrigenics	Patients >65 years	Phase II	French/US placebo-controlled study ongoing. Primary endpoint is overall survival. Target recruitment is 110 patients, half in US and half in France. Results in late 2018 or H119.
Vidaza (azacytidine)/ Celgene	Front-line elderly	Approved in Europe	488-patient study vs conventional care regimens. Median overall survival (OS) was 10.4 months for patients receiving azacytidine compared to 6.5 months for patients receiving CCR. Completed.
Velcade/Takeda + Nexavar/Bayer	Front-line	Phase III	1,250-patient NCI-sponsored study testing various regiments containing bortezomib and sorafenib in parallel in patients with/without mutations. Primary completion date: June 2017.
Vidaza (azacytidine)/ Celgene	CR maintenance	Phase III	460- patient study of oral azacytidine + BSC. Primary completion date: August 2018.
Quizartinib/ Daiichi Sankyo	Relapsed/refractory	Phase III	International Phase III QUANTUM-R trial to treat in FLT3-ITD-positive AML – 363 patients in first relapse. Orphan drug designation in the US and EU and Fast Track designation in the US to treat FLT3-positive patients. Primary completion date: February 2018.
Ivosidenib (AG-120)/ Agios & Celgene	Front-line and relapsed/refractory	Phase I/II	Phase III study in front-line AML in combo with Vidaza to start in H117. First data from ivosidenib Phase I expansion in r/r AML in H117. Phase Ib/II 7+3 study of ivosidenib or enasidenib (AG-221) in combo with chemo in front-line AML ongoing. Phase I/II in combo with Vidaza ongoing in front-line AML. NDA submission by YE17.
PLX3397/ Daiichi Sankyo	Relapsed/refractory	Phase I/II	90-patient Phase I/II trial (patient ≥ 60 years only if unable/unwilling to undergo induction chemotherapy). Primary AML or secondary to an antecedent hematologic disorder. Primary completion in December 2017.

Source: Edison Investment Research, ClinicalTrials.gov

Focus on research and development

Servier collaboration and own programme on track

Hybrigenics and Servier have an ongoing research and development collaboration in the field of deubiquitinating enzymes (DUBs). In particular, the deal involves the validation of one ubiquitin-specific protease (USP) in oncology, screening of lead inhibitors and profiling candidates for further development. Hybrigenics has to date received €4.7m in upfront and research funding and an

additional €2m in milestone-related payments for meeting its research targets. Further potential milestone payments of up to €12m until registration are associated with this programme.

The company has its own programme on DUBs and has independently discovered several series of inhibitors of USP7. Furthermore, Hybrigenics has a strong patent position in the field of USP inhibitors, with five patents granted in the US, EU and Japan, as well as other geographies, with protection until 2032. This programme is excluded from our valuation as it is at an early stage.

R&D services refocus

Hybrigenics announced the disposal via management buyout of a 75.8% stake in Hybrigenics Services, its proteomics subsidiary, for €796k. This includes a €196k upfront payment and three potential payments of up to €200k each, depending on the net result levels achieved by Hybrigenics Services in 2018, 2019 and 2020. Hybrigenics Services generated revenues of €3.5m in 2015 and €3.8m in 2016.

The company retains its Helixio division, which offers genomics, sequencing and bioinformatics services across a broad range of sectors and its Pharma R&D activities including pharmaceuticals, agrofood, cosmetics and environmental industries. Retained services revenues were €2.5m in FY16 (including the Servier €1.5m milestone payment) vs €1.2m in FY15.

Potential in additional indications, pending funding

Chronic lymphocytic leukaemia

Phase II data in early-stage untreated patients with CLL at risk of progression were published in 2014 showing that inecalcitol was able to slow the progression of disease in half of patients. Disease progression is defined by the rate of doubling of blood lymphocyte count (BLC). Out of 21 evaluable CLL patients, 11 experienced stabilisation of disease as measured by BLC, including one patient who achieved a 95% decrease in BLC after 10 months of treatment. This programme is awaiting funding before it begins Phase III trials.

While major advances in first- and second-line treatments have been made in CLL, there has been no change in the treatment guidelines for early-stage patients, which is watchful waiting until symptoms appear. Inecalcitol is positioned as a treatment that can slow disease progression and postpone the need for chemotherapy. Despite improvements in efficacy, chemotherapy may cause limiting side effects in some patients. Inecalcitol has orphan drug status in the US and Europe in CLL. Based on official epidemiology sources, we estimate 30,000 new cases of CLL in the US and EU and potential peak sales of $360m.

Prostate cancer

Inecalcitol also has potential in solid tumours, although the focus is currently on haematology. In a Phase IIa trial inecalcitol was shown to lower PSA levels in patients but survival data is needed to assess the value of inecalcitol in this indication. Development of inecalcitol in prostate cancer has been paused, despite its potential, until additional funding is raised or a partnership is agreed upon. The incidence rate of castration-resistant prostate cancer is around 240,000 new cases a year in the EU. However, the competition has advanced since the trial completed seven years ago, so a potential partner might be more likely to focus on haematology.

Sensitivities

The main sensitivity is the successful development of inecalcitol in haematological cancer. Initial data in CML are encouraging, but the study is open label and has no comparator arm, hence further controlled trials will be necessary to ascertain the value of inecalcitol in this indication. Additionally, this would represent a new approach in the CML treatment paradigm and adoption will be subject to clinical efficacy and physicians' willingness to incorporate it in their practice. Results and progress will also influence Hybrigenics' ability to attract a partnership for follow-on trials in haematological and solid cancers including resuming development in prostate cancer. Hybrigenics has sufficient funds to carry out the Phase II trials in AML and CML, but would rely on further financing or a partnership to progress into further clinical trials in all three haematological indications, and prostate cancer. We have assumed Hybrigenics self-funds development of inecalcitol in leukaemia to approval, which implies a higher royalty on sales than through an earlier-stage partnership, although with higher costs and greater execution risk.

The sale of the proteomic services division, which represented the bulk of revenues, significantly reduces the diversification of Hybrigenics' business model and increases the risk profile of the company.

Financials: FY16 results

Hybrigenics reported FY16 revenue growth of 66% from €2.2m to €3.6m, which includes a milestone payment of €1.5m from Servier in H216, recorded as revenue. Following the R&D reorganisation and sale of the majority of its proteomics services division, the company now reports the results of its retained activities, which include the development of inecalcitol, the research on ubiquitin-specific proteases and its genomic services division Helixio. FY16 genomic services sales increased by 70% from €0.6m to €1m. Our service revenue growth forecast is 40% in FY17, reflecting the rapid growth of this division, and we forecast FY17 services revenue of €1.4m. Total group revenue is expected to remain approximately the same in FY17 at €3.7m as we do not project any milestone payments from Servier.

FY16 operating costs reached €7.1m vs €6.1m in FY15 and we forecast that there will be an increase in FY17 costs to €8m due to additional R&D expenditure on the Phase II trials.

Hybrigenics' net cash position stood at €8.5m as at end December 2016. We estimate this should be sufficient to fund operations into 2018. However, we expect the group to move into a cash shortfall during 2018, which, for the purpose of our model, we have assumed will require new long-term debt of €2m.

Valuation: DCF of €141m

Our risk-adjusted DCF sum-of-the-parts valuation is €141m or €3.9 per share, trimmed from €146m or €4.1 per share, reflecting Hybrigenics' strategy to develop inecalcitol as an orphan treatment in CML and AML in the US and Europe. We have increased the probability of success in CML from 30% to 40% on the back of the positive interim data. Development of inecalcitol in CLL is paused, despite its potential, because Hybrigenics requires funding or a partner to move development forward in this indication. Therefore, we have lowered the probability of success from 30% to 20% and we look to update it in the future depending on the company's plans. We include our forecast of the milestone payments from the collaboration with Servier and our new forecast of sales of the genomics services division Helixio. Preclinical projects and inecalcitol's value in prostate cancer are excluded.

The key assumptions for our DCF valuation are detailed in Exhibit 9.

Exhibit 9: Valuation assumptions for inecalcitol

	Status	Launch date	Peak sales ($m)	Risk adjustment	Market penetration	Royalty
Inecalcitol CLL – US	Phase III ready	2023	180	20%	15%	25%
Inecalcitol CLL – EU	Phase III ready	2023	180	20%	15%	N/A
Inecalcitol CML – EU/US	Phase II	2020	257	40%	15%	25%
Inecalcitol AML – US	Phase II	2020	62	30%	15%	25%
Inecalcitol AML – EU	Phase II	2020	56	30%	15%	N/A

Source: Edison Investment Research

Exhibit 10: rNPV valuation

Driver	Value per share (€)	Value (€m)
Inecalcitol CLL – US	0.5	19.5
Inecalcitol CLL – EU	1.6	58.3
Inecalcitol AML – US	0.3	12.3
Inecalcitol AML – EU	0.9	31.1
Inecalcitol CML	2.1	74.2
Milestones	0.3	12.0
Helixio services division	0.1	3.3
Servier collaboration	0.1	2.3
Risk-adjusted expenses including R&D	(0.8)	(29.2)
Tax	(1.4)	(51.1)
Net cash at end FY16	0.2	8.5
Total	**3.9**	**141.2**
Number of shares		35.8

Source: Edison Investment Research

The changes to our valuation include:

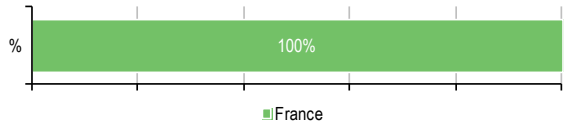
- increasing the probability of success in CML to 40% from 30% due to the positive interim data presented;
- lowering the probability of success in CLL to 20% from 30% until development resumes;
- a new forecast for the genomics services division Helixio;
- adjusting our forecasts, notably estimated risk-adjusted discounted R&D costs for the clinical trials in CML, AML and CLL; SG&A costs for launch in Europe ; and
- updating the net cash position for YE16.

In 2017, Hybrigenics is expected to provide an update on the orphan drug designation for inecalcitol in CML in the EU and the US. The Phase II trial is expected to complete in H218. In addition, the company will present results from the Phase II trial in AML in H119.

Exhibit 11: Financial summary

€'000s	2015	2016	2017e	2018e
Year end 31 December	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	2,172	3,607	3,670	5,598
Cost of sales	(1,104)	(842)	(1,211)	(1,575)
Gross profit	1,068	2,765	2,459	4,023
EBITDA	(4,413)	(3,789)	(4,964)	(3,492)
Operating profit (before GW and except)	(4,563)	(3,908)	(5,083)	(3,611)
Intangible amortisation	(150)	(119)	(119)	(119)
Exceptionals	0	0	0	0
Share-based payments	(225)	(166)	(174)	(183)
Operating profit	(5,016)	(4,319)	(5,502)	(4,039)
Net interest and other financial items	37	30	152	58
Profit before tax (norm)	(4,526)	(3,878)	(4,932)	(3,553)
Profit before tax (reported)	(4,979)	(4,290)	(5,351)	(3,981)
Tax	0	0	0	0
Profit after tax (norm)	(4,526)	(3,878)	(4,932)	(3,552)
Profit after tax (reported)	(4,979)	(4,290)	(5,351)	(3,981)
Discontinued operations	639	(963)	0	0
Net income (norm)	(4,526)	(3,878)	(4,932)	(3,552)
Net income (reported)	(4,340)	(5,254)	(5,351)	(3,981)
Average number of shares outstanding (m)	34.2	35.8	35.8	35.8
EPS - normalised (c)	(13.2)	(10.8)	(13.8)	(9.9)
EPS - FRS 3 (c)	(12.7)	(14.7)	(14.9)	(11.1)
Dividend per share (c)	0.0	0.0	0.0	1.0
Gross margin (%)	49%	77%	67%	72%
EBITDA margin (%)	N/A	N/A	N/A	N/A
Operating margin (before GW and except) (%)	N/A	N/A	N/A	N/A
BALANCE SHEET				
Fixed assets	1,718	1,133	923	707
Intangible assets	820	524	405	286
Tangible assets	585	326	228	130
Investments	313	283	290	291
Current assets	19,584	15,048	8,217	6,725
Stocks	150	55	33	22
Debtors	1,513	546	556	847
Cash	11,716	8,489	3,795	2,024
Other	6,205	3,833	3,833	3,833
Assets held for sale	0	2,125	0	0
Current liabilities	(4,698)	(4,955)	(2,965)	(2,967)
Creditors	(1,727)	(1,565)	(1,727)	(1,726)
Short-term borrowings	(288)	(91)	(91)	(91)
Other	(2,683)	(1,145)	(1,147)	(1,150)
Liabilities associated with assets held for sale	0	(2,154)	0	0
Non-current liabilities	(629)	(346)	(346)	(2,346)
Long-term borrowings	(114)	0	0	(2,000)
Other	(515)	(346)	(346)	(346)
Net assets	15,976	10,881	5,828	2,120
CASH FLOW				
Operating cash flow	(5,304)	(2,593)	(4,790)	(3,773)
Net interest	56	34	152	58
Tax	0	0	0	0
Capex	(548)	(274)	(147)	(147)
Payment of deferred consideration	0	0	0	0
Capitalisation of development costs	0	0	0	0
Expenditure on intangibles	0	0	0	0
Acquisitions/disposals	0	0	0	0
Financing	8,457	0	0	0
Dividends	0	0	0	0
Net cash flow	2,661	(2,833)	(4,785)	(3,862)
Opening net debt/(cash)	(9,644)	(11,602)	(8,489)	(3,795)
HP finance leases initiated	0	0	0	0
Other	(703)	(280)	91	91
Closing net debt/(cash)	(11,602)	(8,489)	(3,795)	(24)

Source: Edison Investment Research, Hybrigenics accounts. Note: Accounts have been restated to reflect the sale of a controlling stake in Hybrigenics Services.

Contact details	Revenue by geography
3-5 impasse Reille 75014 Paris France +33 (0)1 58 10 38 00 www.hybrigenics.com	

Management team

CEO: Rémi Delansorne	CMO: Jean-François Dufour-Lamartinie MD
Rémi Delansorne has been CEO since September 2005 (director since October 2007), having joined Hybrigenics as director of R&D in 2004. Previously he was with Théramex, a French subsidiary of Merck, latterly as director of research in diabetology. He holds a DVM from National Veterinary School of Alfort, France, and a PhD in biology from the Université Pierre et Marie Curie.	Jean-François Dufour-Lamartinie joined Hybrigenics as head of clinical research in 2006. He has broad experience of clinical development, having been a clinician at various cancer research institutes including Institut Gustave Roussy and clinical research director of BioAlliance Pharma, prior to joining Hybrigenics.
CFO: Guillaume Floch	**Chairman: Alain Muñoz**
Guillaume Floch has been CFO since June 2008. Previously he was head of business planning and performance of Cephalon (France), and financial controller of Zeneus Pharma and Elan France.	Alain Muñoz became chairman of Hybrigenics in July 2015. He also serves on the boards of biopharmaceutical companies Auris Medical, Valneva and Zealand Pharma. Previous roles include chairman at Novagali Pharma and board membership at Erytech.

Principal shareholders	(%)
Pradeyrol Development	3.6
Life Science Partners	2.4

Companies named in this report

Celgene (CELG, US), Agios (AGIO, US), Bayer (BAYN, GR), Sankyo (6417, JP).

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