CARMAT

N°4 - July 2013

shareholder newsletter

A word from the CEO

Dear shareholders,

The 1st half of 2013 saw some major milestones for our project, both financially and scientifically. Indeed, at the end of the half-year we strengthened our financial situation via the signing of a contingent equity line agreement with Kepler Cheuvreux concerning a maximum of 200,000 new shares, representing a potential dilution of no more than 4.81%. This very flexible deal can be used at any time, and comes in addition to our cash position, which stood at €9.2 million at May 31, 2013. CARMAT thus has the necessary means to carry out its clinical development.

Of course the biggest announcement during the half concerned the approval to proceed with the first human implants of our bioprosthetic artificial heart at four international cardiac surgery centres. Excellence being our primary criterion, each of these centres is a leader in its country and has an international reputation.

This newsletter*, our fourth, thus provides us with an excellent opportunity to present one of these centres, the Silesian Center for Heart Diseases in Zabrze, Poland, via an interview with Professor Marian Zembala (Director of the Silesian Center for Heart Disease, Chairman of its Department of Cardiac Surgery and an alumnus of Professor Alain Carpentier).

CARMAT has put in place an international clinical trial strategy, thus complying with best practices in this field. However, the desire to carry out implants in France, the country where this unique project and world first was born, remains as strong as ever. Our efforts aimed at reaching this objective were intense throughout the half, and enabled substantial progress to be made with regard to the ANSM's demands, with further in-vivo tests on calves. You have asked many questions about these tests, their relevance and their place in our clinical program. The interview with Dr Luca Zilberstein, Associate Professor Anaesthesiology & Critical Care, Head of the Anaesthesia Unit at the Ecole Nationale Vétérinaire veterinary school in Maisons-Alfort, will explain the challenges and limitations of using animals as models when preparing for human trials.

Lastly, it gives us great pleasure to be able to present, in this newsletter, one of the cornerstones of our project of which we are particularly proud: the CARMAT test benches and simulators. Inspired by the aerospace industry, they are the result of work carried out by teams of experts who have managed to create an artificial environment simulating the human body to test our prosthesis.

I would like to thank all of these people, our project's stakeholders and of course our shareholders for their staunch support that is enabling us to move ever nearer to our objective of finally seeing the CARMAT heart save lives.

Marcello Conviti
CEO

** Readers are invited to consult the caution note included in the Company's press releases*

H1 2013 key events

March	Annual results show a cash position of €11.1m at December 31, 2012
April	€5m in Research Tax Credit received pertaining to 2012
May	CARMAT receives approval to carry out the 1st human implants of its bioprosthetic artificial heart at 4 cardiac surgery centres in 4 countries
June	Setting up of a contingent equity line

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Pouch and membrane endurance test bench room

Each critical component or subcomponent of the CARMAT heart and the complete system have been tested using the aerospace industry's 21st century standards, thanks to sophisticated and customised test benches and simulators whose development entailed a number of projects in themselves:

- 29 companies*, institutions and laboratories having contributed to tests or the development of benches and simulators;
- 224 staff or subcontractors involved internally in bench and simulator tests;
- 35 test benches for components, subgroups and systems;
- 10 test benches in production;
- 6 simulators (of the prosthesis, bloodstream, haemodynamic and mechanical).

* CARMAT would like to thank all the partners and suppliers who have contributed to developing our test benches and simulators, and in particular Altair, Astrium, ATEC, Axon, Charles River, CEMIOS, the Nantes university hospital, CRITT, EMITECH, ENVA, Filab, Haemolab, Haemoscan, HEF, HEGP, Inoprod, LNE, LCIE, Matra Electronique, ONERA, ONIIRIS, Oskman, PolymerExpert, Protomed, RESCOLL, SERMA, Vignal Artru Industries, Université Lyon 1, etc.

The point of view of the clinician:

Clinical research on innovation is a duty to our patients

An interview with Pr Marian Zembala cardiovascular and transplant surgeon, Director of the Silesian Center for Heart Disease in Zabrze, Poland, and Chairman of its Department of Cardiac Surgery.

Professor, could you tell us about the Silesian Center for Heart Disease and your activity in the surgical treatment of heart failure in Poland?

The Silesian Center for Heart Disease (SCCS) is an internationally recognized, highly specialized academic clinical and scientific center, affiliated with the Silesian Medical University that focuses exclusively on the treatment of heart, lung and vascular diseases in children and adults. It is located in Zabrze, in Silesia Province (population of 6 million) in the south of Poland, close to Katowice and Krakow.

Cardiovascular disease is the leading cause of death in Central and Eastern Europe, far above all other causes including all major cancer types. For example the incidence of coronary disease is nearly 3 times higher in Poland than in France. Apart from that, due to the development of invasive cardiology and cardiac surgery, we have recorded a substantial reduction in mortality among patients with acute coronary syndrome. It has been reduced to a similar level to that of Denmark and Sweden. Even though the number of deaths caused by coronary disease has been halved in the last decade, just like in most developed countries, many surviving patients develop progressive and chronic heart failure due to the persistence of underlying causes such as high blood pressure.

The Silesian Center for Heart Disease

The Silesian Center for Heart Disease admits almost 15,000 patients each year, performing 2,400 cardiac operations. It is the largest heart failure and heart and lung transplant center in Poland, well known for its unique chronic heart failure program. Since 1985 it has performed more than 33,000 heart surgeries and more than 1,000 heart and 90 lung transplants, with 40-50 heart transplants a year. Since 1988, due to the limited number of cardiac donors, we have gained significant experience in ventricular assistance devices.

How did you come to agree to a clinical partnership with CARMAT?

I believe that in medicine and surgery, being at the forefront of clinical research is nothing more than a duty to our patients. As such, our center has a history of pioneering new technologies. In Poland, we were the first hospital to introduce primary angioplasty for acute coronary syndrome (1985), we performed the first heart (1985), lung (1987) and heart-lung (1986) transplants, the first implantation of a mechanical circulatory device (1987) incl. ECMO and VAD, closure post infarction VSD (2002), modern arterial revascularization, mini-invasive coronary (TECAB hybrid) ablation, first implant of a transcatheter aortic valve. We were the first to treat acute respiratory distress syndrome in infants with extracorporeal membranous oxygenation systems, opened the first intensive coronary care unit offering 24/7 invasive treatment, and developed the first surgical endo and epicardial ablation program for cardiac arrhythmias and hybrid ablation for permanent atrial fibrillation.

We also developed the largest mitral valve repair program in Poland, and I have the honor and pleasure of being an alumnus of Professor A. Carpentier's course on mitral valve repair.

An innovative artificial heart - the need for which is great - that associates Professor Carpentier's vision with the expertise of a large industrial partner can only be appealing. We were presented with attractive bench and animal studies. The decision to participate in the pioneering clinical implants was therefore an easy one to make. Since then, our teams have gone through an intensive training program. I personally attended animal implants in Paris last month with our surgical team, and was impressed by how close the procedure is to heart transplants. Frankly speaking, this cooperation is a kind of distinction for our center, as it involves extensive admiration of Professor A. Carpentier and his team for their creativity and the genuineness of their research and development, so important for contemporary cardiac and vascular medicine.

What patient profile would you consider for the feasibility study?

Due to the insufficient number of donors and the stringent criteria to be eligible for a heart transplant, many patients are denied life-saving treatment. The ideal patients for these first trials should of course have no other option for obvious ethical reasons, but should also have a good hope of recovery thanks to the artificial heart, that is to say that their other organs such as their kidneys and liver, should not be irremediably damaged. Otherwise, it would be difficult to judge if an issue should be attributed to the prosthesis or to the patient's prior status. For example, active cancer is a strict contra-indication for a transplant: a relatively young patient with a limited life expectancy due to myocardial cancer would be an ideal candidate.

When will the SCCS be ready to implant?

The patient selection process has begun. We are ready and very eager to start. The most important thing here is that, in Poland too, patients are waiting for the possibility of this kind of treatment.

Focus on test benches and simulators

The test strategy has been one of the aerospace industry's major contributions to the CARMAT project: could you tell us a bit more?

The CARMAT heart has a large number of critical functional components and subgroups, just like an aeroplane or a satellite. Similarly, they have to meet stringent requirements in terms of the way they operate and their reliability. We therefore needed to develop the means to validate these requirements at every stage of their design, development and then production. In addition to these constraints, relatively standard in the aerospace sector, we also needed to simulate the environment in which the prosthesis will operate, i.e. the human body. It was this unique aspect that our teams worked on. As well as the usual validation of the mechanical or electronic parts, which are already highly sophisticated, we had to design innovative and customised means of validation to test all moving parts or those in contact with the blood, usually in collaboration with doctors who are cardiac physiology specialists.

What types of benches and simulators have you developed?

There are various categories of benches. Firstly, those that perform a specific test regarding, for example, endurance, the electronics, the sensors or the biomembrane. In these cases, we're not looking to represent an entire context; we're simply trying to test the behaviour or characteristics of a single component. It may appear simple but, given the specificities of the heart's components, it isn't. For example, to test the endurance of the biosynthetic membrane on the blood side, pericardium, on the pump side, polyurethane), 65 cc (the ventricular volume) has to be pumped at 10 Hz, 24/7 over a number of years on 8 autonomous benches working in parallel. You therefore need an enormous compressor that takes up almost a half of the test room (see the photo on page 1), without counting the cooling system, outside. We're at the extreme limits of what a hydraulic system can achieve!

Then there are the benches that simulate a complex real-life entity, where we are trying to be as close as possible to the entire object being studied such as the prosthesis, human body, bloodstream, etc.

Could you explain the difference between real-life tests and virtual tests?

With virtual tests, it's just software modelling, with no physical action. Such modelling is irreplaceable when

Focus on the animal model:
Like a quiet day's sailing that turns into a round-the-world trip

Interview with Dr Luca Zilberstein, Dipl ECVAA, DVM, PhD, Associate Professor Anaesthesiology & Critical Care, Head of the Anaesthesia Unit

Doctor, could you tell us about ENVA and your involvement in the CARMAT project?

ENVA, the Alfort Veterinary School, was founded in 1765: it is the world's oldest veterinary school still located on its original site. It receives more than 35,000 animals a year on its 3 sites, one of which is in the Yonne region and is dedicated to farm animals. It's also a research centre that notably specialises in animal models' physiology and physiopathology. When we were approached by CARMAT, the aim appeared to be a simple one: a few animals, over a short timeframe, essentially to train surgeons and teams in gestures and procedures. The ANSM's additional requirements meant that all of this had to be completely reviewed. Instead of having to monitor a handful of animals for 48 hours, there were now over a dozen conscious animals monitored 24/7 by a medical-veterinary team of specialists in anaesthesia, reanimation, cardiology, etc.

The Veterinary University Hospital at Maison-Alfort

Talk about a small project becoming an immense one – it was like a quiet day's sailing that turns into a round-the-world ocean-racing trip! We successfully coped with the challenge and its difficulties, although with hindsight I must admit that if we'd known all it would entail then we might have thought twice before agreeing to participate!

What sort of difficulties were there?

We encountered a number of scientific and medical difficulties. Firstly, this was pure experimentation. These types of trials on cattle had already taken place for assist devices or artificial hearts, but there was no precedent in France and no published study on extracorporeal circulation – a heart-lung bypass machine – on calves. Being farm animals, heart problems are rarely treated surgically because the cost just doesn't make it worthwhile. We had to start from zero, learn and alter our approach as the experiment progressed.

We also only had one possible model of animal because of size issues: calves. And these are very complex animals: four stomachs, ruminants, herbivorous, rapid growth, etc. The right window in terms of the animal's suitability for the prosthesis, i.e. 100 to 120 Kg or 2 to 3 months, corresponds to the animal's weaning phase, in other words the period when it goes from drinking its mother's milk to eating grass, which gives rise to glycaemia problems.

At this young age, the animal's major organs – kidneys, liver, brain – are not yet properly functional. We also had to choose a "meat bread", because they have a more developed thorax that is better-suited to the prosthesis, but these animals also have a large muscular mass, which implies a greater cardiac output of up to 15 litres a minute, or almost 170% of the prosthesis' maximum output.

Because of this, all of the implanted animals were immediately in heart failure that gradually worsened as the calves grew and their metabolic requirements increased. Longer-term monitoring was therefore inconceivable. Even at this size and weight, there were pulmonary compression problems because of the major anatomical differences between a calf and a human. So with a large thorax we had circulation problems (not enough output), whilst with a smaller thorax there were ventilation problems (compression of the lungs): squaring the circle.

Did you encounter any surgical difficulties?

Yes, inevitably, because of the major anatomical differences, although the highly-experienced surgeons were able to overcome them. In fact we could justifiably ask whether this model is really transposable insofar as there is no anatomical suitability, an insufficient output, a very different physiology… Of course it is quite right to take precautions before implanting the device into a human, but is this the right precaution? In any case, one thing is certain and that's the fact that, thanks to these tests, we know that the prosthesis works properly: none of the prostheses failed despite the maximum output and complex procedures.

In conclusion, how would you describe this experience?

Just one word to describe the CARMAT experience: extraordinary, despite all the difficulties. Extraordinary from a scientific perspective: being involved in making a dream become reality and an opportunity that only comes along once in a lifetime. And even more extraordinary from a human perspective, thanks to incredible teamwork involving a variety of cultures, people and scientific backgrounds. I'd especially like to thank my veterinary team, and in particular Dr Thomas Lilin and Dr Guillaume Belbis, as well as Professor Bernard Cholley and Dr Denis Méléard from the HEGP Anaesthesiology & Critical Care department. If we had to do it all again, we would, albeit more serenely because of the experience we have acquired. And then there's the national pride aspect of having worked on a unique product that has been designed, developed and tested in France.

– interview with Paul Kohler, Head of the Algorithms and Functional division

testing situations that couldn't be tested on a physical bench and even less so on a human being, such as extreme high or low pressure. These virtual benches also help avoid the consumption of expensive components such as the motors or sensors, by simulating them, and thus allow all pre-tests to be carried out before launching the manufacturing of a customised bench. Our HIL (Hardware In the Loop) virtual bench, for example, isn't very photogenic but it is very useful. It's a big black box linked up to a PC. The PC simulates the prosthesis, and the electronics inside the black box simulate the human body. By downloading the prosthesis software, we can test, at a relatively low cost, a lot of hypotheses that would be difficult or impossible to physically test, such as what happens if a motor breaks or if a sensor stops working. We basically simulate the actuators' response to the sensors with mathematical equations. Real-life tests, as the name suggests, make it possible to test an actual object, such as the prosthesis, in an environment that is as close as possible to real life.

Advanced haemodynamic bench

Which bench are you most proud of?

Definitely the advanced haemodynamic bench, which reproduces the bloodstream. It's the bench for which we spent the most time talking to doctors, because it enables us to validate the automatic response to patients' needs by simulating physiological life cycles, such as a normal day but also pathological situations such as a haemorrhage. It's our most-advanced bench and takes into account all of our experience on other tests, real-life or virtual, as it allows you to choose one of three operating modes: 100% simulated, the actual auto-regulation software with everything else simulated, and 100% real-life with a real prosthesis and its controller.

What incited you to join CARMAT and lead this division?

I joined the CARMAT Economic Interest Group as a contractor 11 years ago. When the Company was created in 2008, I quite logically joined it. I have a Masters degree in industrial IT and electrical engineering. Before Matra, I also worked with Oseo's predecessor, the Anvar to help facilitate the transfer from academic research to industry, and developed experience in interdisciplinary projects combining electronics, mechanics and IT.

CARMAT and the stock market
at June 30, 2013

Share price (closing): **€112.68**
Number of shares: **4,169.895**
Free float: **27.9%**

Name: **CARMAT**
Ticker: **ALCAR**
ISIN code: **FR0010907956**

ALCAR
LISTED
NYSE
ALTERNEXT.

Share performance at June 30, 2013

Change in share price: **-11.54**% (Alternext: +1.73% / CAC 40: +2.69%)

Liquidity: **6,235 shares a day** on average over the half-year

Shareholders' questions

Will the first human implant take place in France, or in another country?
The establishment of clinical agreements abroad meets two objectives. Firstly, setting up an international multicentre study represents a clinical best practice. It enables any possible bias resulting from a trial being carried out in a single centre or single country to be eliminated. Secondly, it helps provide a global base for a product that is not intended to be limited to its domestic market, as heart failure is a global health issue.

Since the announcement of the clinical agreement with the four chosen centres, we have made significant progress in training the medical teams and choosing the patients. Instigating this multi-country strategy has reaffirmed our ability to operate highly efficiently abroad and to interact with local teams, backed by extensively-trained and experienced French teams. This strategy in no way affects our intention of carrying out clinical trials in France, although at this stage we cannot predict the nationality of the first patient who will receive our artificial heart.

When should we expect this first implant?
As things stand, the schedule presented in the last reference document remains unchanged. We are still hoping to finalise the first clinical phase, the feasibility study, during the second half of this year in order to obtain the necessary authorisations to begin the second clinical phase, the pivotal study, before the end of the year.

Why have you set up a contingent equity line, which would have a dilutive effect on capital?
We want these two clinical trial phases to be carried out quickly and under the best possible conditions. That's why we wanted to secure our financial structure beforehand in order to be able to mobilise the necessary funds depending on the requirements of each of these clinical phases. A number of options were looked into, but it was the contingent equity line that the Board agreed on. This solution was deemed to be the most efficient compared to the costs that would result from a traditional capital increase, and its dilutive effect will be no more than 4.81%, given the maximum of 200,000 new shares that could potentially be issued over the 2 years this agreement is valid for. Moreover, CARMAT gets to choose the dates and quantities of each drawdown depending on the project's progress.

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Financial agenda

Monday, September 2, 2013
2013 half-year results

CARMAT in the media

LE SOIR
May 16, 2013
"Implanting an artificial heart that is just like a human heart in every respect could be about to become a reality. Indeed, this Tuesday French company CARMAT received approval to carry out the first human implants of its artificial heart."

Le Monde
May 16, 2013
"If all goes well, the commercial launch could take place in 2015, or maybe even next year. The shareholders who have been supporting this 100% French innovation should then begin to reap the financial benefits."

Aujourd'hui en France
May 16, 2013
"[...] around twenty conclusive tests carried out in European facilities will allow CARMAT to obtain CE Mark, which is synonymous with being able to launch the product on the European market – and hence the French market, with thousands of patients concerned."

la Croix
May 15, 2013
"French company CARMAT, which is developing a totally artificial heart, has just obtained the approval of four cardiac surgery centres to carry out the first human implants."

LE FIGARO
May 15, 2013
"The artificial heart developed by this young high-tech company based in Vélizy [southwest Paris suburbs] aims to solve the issue of a lack of donor organs that is a real problem for patients suffering from advanced heart failure. Over 20 million people in Europe and the United States are currently affected by this illness."

Les Echos
Le Quotidien de l'Economie
May 14, 2013
"The dream of eminent heart surgeon Alain Carpentier, who has invented the totally implantable artificial heart, is about to become a reality following twenty years of relentless development."