N°5 - February 2014

shareholder newsletter

A word from the CEO

Dear shareholders,

It is with considerable emotion that I am addressing you through this fifth edition of our Newsletter. The end of 2013 saw the efforts of all those who have believed in the CARMAT project materialized in the best possible way: the 1st human implant of our bioprosthetic artificial heart. This medical exploit, a world first and the result of Professor Carpentier's vision, has become a reality thanks to the total commitment of the CARMAT teams, the strong support of our industrial and financial partners, the prowess of the medical teams involved, the bravery of the patient and, of course, the trust of all our shareholders who have backed this project over recent years. I would like to thank all of these people as we begin a new year, which sees CARMAT enter a new phase in its history: a phase of clinical development and validation.

I would like to invite you to take a behind-the-scenes look at this world first as it was experienced by various stakeholders. Beforehand, via the figures to the bottom right of this page, you can judge the breadth of the requirements of such an operation for yourselves.

I then invite you to read the interview with Professor Bernard Cholley, Deputy Head of the Anesthesia-Resuscitation department at the Georges Pompidou European Hospital (HEGP), who gives us his expert perspective on this innovation and the importance of the phase that follows the implant. Indeed, the first weeks after the patient awakes are the most crucial.

You can also read about the activities of our Clinical department, headed by Antoine Capel, which provides the hospital teams with operational support in order to ensure a fluid implant procedure and monitor the prosthesis within the patient's body to make sure it is operating correctly.

There is then an interview with IREIS – HEF Group, one of our longstanding partners and party to the contract signed with Bpifrance, that will allow you to gauge the efforts that this tribology specialist, which has worked alongside CARMAT for over a decade, has put into the long-term durability of the device that lies at the very heart of our prosthesis; the pump unit.

Four patients have to receive implants in order for this first study to be finalized. It will only be after they have been closely monitored for 30 days that we will be able to draw conclusions. If the results are positive, we will be able to move on to the European pivotal study that should enable us to obtain CE Marking in Europe within about two years. After this, or simultaneously, we will have to apply for IDE (Investigational Device Exemption) approval from the American health authority (FDA) to carry out a further clinical trial, before obtaining premarketing approval (PMA) for the CARMAT heart in the United States. This process can take from 2 to 5 years. There are therefore still some exciting key milestones ahead to share with you.

On behalf of the Company, I would like to express our gratitude for the perseverance and support with which you have been following our project, and of course wish you all the best for 2014.

Marcello Conviti
CEO

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

H2 2013 key events

July	€6.7m received from Bpifrance
September	Half-year results show a cash position of €8.5m at June 30, 2013
	CARMAT receives ANSM approval to carry out implants of its artificial heart on patients in France
October	CARMAT participates in the 27th EACTS Annual Meeting in Vienna (Austria)
December	First-in-man implant of CARMAT's bioprosthetic artificial heart

Contents

The 1st implant in figures

2 hours 49 minutes: time on the heart-lung bypass machine

This is equivalent to a heart transplant with no complications. The shorter the time, the lower the risk of complications, notably neurological.

12 : hospital or technical staff allowed into the operating theater

2 heart surgeons, 2 perfusionists responsible for the bypass machine, 2 anesthetists-resuscitators, 3 IBODE and 3 members of CARMAT's clinical team.*

8 : CARMAT staff on 24/7 standby during the trials

2 : independent study supervision and analysis committees

1 *critical event committee (CEC): 3 health professionals, completely independent of CARMAT or the hospitals approved for the trial, to assess any complication.*

1 *Data and Safety Monitoring Board (DSMB): 3 health professionals, completely independent of CARMAT or the hospitals approved for the trial, to assess compliance with the protocol.*

These committees independently decide whether the study should be halted or may be continued.

2 : complete systems available in the operating theater
This allows total redundancy should, for example, one of the system's components be accidentally desterilized. This includes every part of the prosthesis, the implant tools, cables and consoles, i.e. more than 40 references for each complete system.

** Infirmiers de Bloc Opératoire Diplômés d'État* (state-registered operating theater nurses)

The point of view of the clinician:

A real step forward to help end-stage heart failure patients

Interview with Professor Bernard Cholley, Deputy Head of the Anesthesia-Resuscitation department at the Georges Pompidou European Hospital (HEGP), AP-HP and Professor of Anesthesia-Resuscitation at René Descartes-Sorbonne Paris Cité University

When did you find out about the CARMAT project?

I work at the HEGP in close collaboration with Professor Fabiani's cardiovascular surgery teams, and am in regular contact with all of the project's players. It's been over 5 years since Professor Carpentier asked me to become involved. I then met with CARMAT engineers to discuss the issues of venous return and cardiac output, and I was contacted again for the animal testing phase. Professor Carpentier wanted the teams who would be carry out the first human implants to be stakeholders in all of the tests on animals.

Did you encounter any difficulties during the animal testing?

It was a unifying project, an intense period. There was an amazing spirit; everybody was very enthusiastic, the HEGP doctors, the CARMAT engineers, the Maisons-Alfort veterinary surgeons, etc. We knew that it would lead to a milestone event. Obviously, it's a lot more complicated undertaking such operations on a calf than on a person: the prosthesis has been designed for humans. For a resuscitator, who has to monitor the operation, you have to take into account the fact that the animal will lie on its scar, for example, and that there will be asepsis issues that don't occur with humans. We also know that a calf has a much higher cardiac output than a human, beyond the limit of what the prosthesis can cope with. This has enabled us to get to know the tool well, how to manipulate it and to anticipate surgical outcomes.

Where does the role of an anesthetist-resuscitator start and end, with regard to implanting the artificial heart?

The anesthesia-resuscitation team is involved before, during and after surgery. Before the patient even goes into the operating theater, you have to carefully consider their general state. It's a crucial phase for success, during which surgeons, cardiologists and anesthesia-resuscitation doctors assess the patient and the potential risks: you must try to anticipate any issue that could arise; we therefore talk to each other a lot! The surgeons ask our opinion on the patient's general state, and notably their organs other than the failing heart that supports them. The keyword is teamwork; the medical-surgical team.

And on the day itself?

Obviously we follow the patient in the operating theater; a key stage where everything has to go smoothly. As this is a first, the procedure is not yet totally perfected: we don't know where pitfalls may lie or where problems may arise. The anesthetist's "resuscitation" role is crucial: any heart surgery that involves extracorporeal blood circulation has a high hemorrhagic risk, additional blood products have to be provided, the right amount, no more… It's a very delicate phase, the patient's blood flow is diverted to an external heart/lung machine, there is substantial dialogue with the perfusionists regarding the flow and pressure. The perfusion – irrigation in blood of all of the other organs such as the brain, kidneys and liver – has to be optimal during this phase to avoid post-operative issues. For this intervention, I was in the operating theater with Dr Méléard – who was also heavily involved in the animal testing – and an anesthetics nurse. There were a considerable number of uncertainties: we were all extremely vigilant, we were aware that we didn't yet have the automatic reflexes of routine operations. We monitored the patient minute by minute, as you might watch milk on a stove.

How did the awakening of the patient go?

You first have to make sure that the patient is stable and that there is no need to return to the operating theater before wakening the patient. Once everything was stabilized, the awakening went very well and we were able to extubate the patient soon thereafter. As this operation was the first of its kind, the monitoring of the first few weeks is the most critical period, as the patient's improvement can be peppered by various complications. There are still unresolved issues such as the anticoagulation management: with no previous experience to call on, it is difficult to know whether these drugs are beneficial or detrimental.

What stood out for you in this first implant?

It's extraordinary to work at the very limits of medicine, to use a brand new technology to help a patient. We know that a large number of patients face a tragic situation because their heart is failing and they are experiencing pre-terminal circulatory failure. They are praying for an organ to which they may well never have access to, given the very strict rules governing eligibility and the small number of grafts available. If we have an alternative to help these people rather than just watching them die, it will be a real step forward. There are risks, of course, but our goal is to secure a real benefit for patients and to reach the stage when this operation will be part of our routine, once we have gathered the needed experience.

The Georges Pompidou European Hospital in Paris (France)

The point of view of the partner:

Extending patients' life thanks to tribology

Interview with Mr Maurin-Perrier, President of IREIS, HEF Group.

Mr Maurin-Perrier, could you tell us about IREIS?

The *Institut de Recherches En Ingénierie des Surfaces* (IREIS, the Surface Engineering Research Institute) is a contract research company for the HEF group's companies and external clients, and is based just outside St Etienne. Our activity focuses on tribology*, which studies the interactions between two material systems in contact, whether static or in motion: friction, wear and tear, lubrication etc. Since 1953, we have acquired substantial experience through over 2,500 studies in the automotive, aeronautical, energy and consumer products sectors. Some topics we look at are close to people's daily lives, such as the efficient friction-action of your sponge, whilst others are exceptional, such as the wear and tear of earthquake-protection systems or the pump unit at the heart of the CARMAT prosthesis.

What is the nature of your partnership with CARMAT?

We have worked alongside CARMAT since before its creation in 2008 or the start of the project financed by Bpifrance in 2009. Back in 2003, we began work on the wear and tear and endurance of the pump unit with the engineers at Matra (Airbus Group). We are more than a subcontractor, acting as a real long-term partner with the financial and human involvement this entails. For example, part of the work is financed with no margin within the framework of the Bpifrance contract, and we have designed and built a special laboratory with secure, airtight and air-conditioned rooms. All in all, 12 of our 60 employees have worked on the CARMAT project at one time or another, with up to 4 or 5 staff working on it fulltime at any given moment during the qualification period.

What is IREIS' role in the development of the CARMAT artificial heart?

The prosthesis contains numerous biological or mechanical components that are moving constantly. We focused on the mechanical aspects of a most critical component, the pump unit that activates the fluid that in turn enables the biomembranes to move, and hence the blood to flow. Any premature blockage or premature wear could be fatal to the patient. It comprises a 'squirrel-cage' actuator working in extreme conditions – it continually rotates 9,000 times a minute and has to change direction at least once a second, in line with the patient's heartbeat.

Endurance testing bench for the motor-pump unit

IREIS defined and developed the necessary means to implement the pump unit's validation test: a long-term undertaking that is still on-going in order to supply CARMAT with the required endurance and reliability data. The initial list of specifications focused on substantially improving the durability – from just a few months for the first prototypes. The first improved systems dating from 2004-2005 are still working on our benches and are performing perfectly well.

What constraints did you have to overcome to achieve this result?

We first worked on defining the materials in order to reduce wear and tear without affecting friction. Indeed, wear and tear reduces durability and friction affects efficiency, and notably the autonomy provided by the batteries because you consume more energy: we needed to find the right balance. Firstly, we developed the means to simulate wear and tear and friction, and then we modelled these interactions to understand their behavior and forecast the lifespan. We're talking about well-known and mastered materials, but used in extreme conditions.

As a specialist, what's your opinion of the pump unit's endurance today?

The pump unit is a complex functional sub-unit comprising micromechanics and electronics, but the latest stringent tests couldn't reveal any notable wear and tear. The goal was to obtain validated endurance corresponding to the survival of a 60 year old transplanted patient, i.e. a system that will last for at least 10 years. My opinion is that the current pump unit comfortably meets these requirements: 15 years, 20 years, 30 years… only long-term clinical experience will provide the answer.

What does the CARMAT project represent for you?

It's a project during which we learned a lot, and that also includes a substantial emotional aspect. In terms of the experience acquired, this quite unique project has enabled us to create a bridge between experimentation and modeling, which is fairly rare in our field of tribology: we not only had to observe complex multiphysics phenomena, but also be capable of modeling them in order to improve them. More importantly, it's a very special project: it's amazing to be able to contribute to saving lives and to tell yourself that you're working not to improve the lifespan of a machine, however useful that machine may be, but to extend people's lives by years.

** from the Greek tribein (to rub) and logos (study of, knowledge of)*

Focus on hospital operational support

- Interview with Antoine Capel, Head of the Clinical department

What is your role within CARMAT's organization?

The Medical division, headed by Dr Piet Jansen, comprises two departments: a Clinical and Regulatory Affairs department (relations with the authorities, clinical trial application dossiers and gathering of data and dossiers after the trials) and the Clinical department that I am honored to steer. My team's role was and still is very broad. In the preclinical phase, we defined, set up and executed all of the anatomical compatibility tests, with the development and validation of our virtual implant tool, and all of the biological tests. This broad term covers the haemocompatibility tests for the biological materials, all of the tests carried out on calves, the development of the surgical technique via ex-vivo studies, and all relations with the medical and veterinary teams, for the setting up and steering of training and its validation on animals. Since we have begun the clinical phase, we are in charge of all of the implant's operational aspects. This incorporates every stage before, during and after the implant, from the modeling of the pre-implant anatomical compatibility, the management of all the prosthetic materials that need to be in the operating theater on the day of the operation, our presence in the theater - to support the hospital's personnel - and all the post-operative technical and clinical support during the monitoring phase. Our team currently consists of 6 people.

How did you access this essential position?

Through the backdoor! I was finishing a dual postgraduate course in Bordeaux (DEA degree in human biology / DESS degree in biomaterials) and in early 2003 was astoundingly lucky and obtained an internship in Professor Carpentier's Biosurgical Research Laboratory, where I worked on the properties of bovine pericardium. I have immense respect for the Professor, having had the amazing opportunity of working alongside him through all these years, an opportunity many seasoned surgeons would give their right arm for. He has so many ideas and is always thinking about the next step: he can be hard to keep up with! Backed by this experience, I then joined the CARMAT General Interest Group to work with Matra's engineers on other biocompatible materials that can be used in conjunction with pericardium. We tested their mechanical resistance, characterized their physicochemical properties, etc. Joining the Company when it was founded was a natural step.

Over all these years, did you experience times of doubt or gloom?

My motivation has always held up and I've never had any doubts regarding the artificial heart or the bioprosthetic technologies used. The only difficult period was early 2008, before the Company was created and new investors came onboard. We had to fight to obtain financing, the future was uncertain, we spent a lot of time presenting our project. The arrival of Truffle Capital in 2008 and the massive support of Bpifrance in 2009 boosted the morale of all of us, including me. I can't emphasize enough that CARMAT was and remains an opportunity to work with truly exceptional people on extraordinary technologies.

How did you experience the first implant?

On the day itself, I wasn't even sure I'd be allowed into the operating theater! Professor Carpentier had drawn up a list restricted to people whose presence was absolutely essential and three people from my team were already involved. I wasn't really worried; I was more focused on all the little details and being on my toes. The operation had been extremely well prepared: over the previous six months, we had carried out over a dozen implants in calves with this team, one every two weeks! We all surpassed ourselves, but we were confident, we knew that we could do it, that the CARMAT team and the medical/surgical team were in perfect shape.

And now?

The first implant is a huge milestone and a very important moment for me. After all, CARMAT is the first and only company I have ever worked for, and my life has been devoted to this project for the last decade or more. The following day, I was lucky enough to be there to see the patient wake up, thank us all, shake my hand… It was a unique moment I will probably never experience again.

In the operating theater with Pr Carpentier

We are all aware that this is just the beginning of a new phase, not the end of our journey. In 2008, we experienced a new beginning with the creation of the Company. My work has evolved: fewer validations in the laboratory, more practical applications, management, contact with doctors… In 2013, this first implant represented another key milestone for the Company and no doubt for my professional life too, with new challenges awaiting, notably abroad.

CARMAT and the stock market
at December 31, 2013

Share price (closing): **€116.60**
Name: **CARMAT**
Ticker: **ALCAR**
ISIN code: **FR0010907956**

ALCAR
LISTED
NYSE
ALTERNEXT.

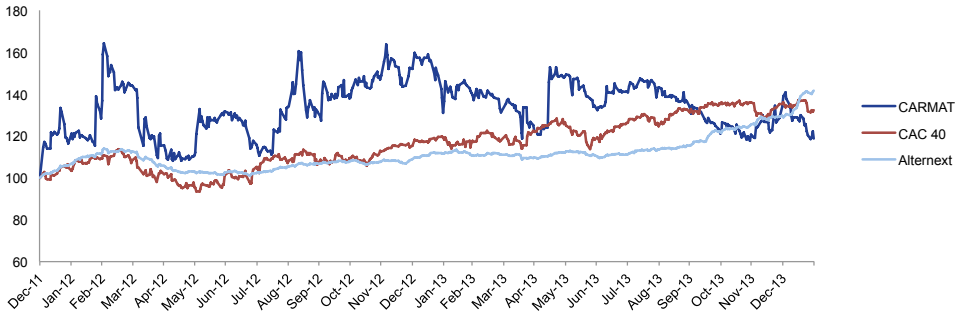
2013 share performance

Change in share price: -8,46%

Liquidity:

- **8,478 shares a day** on average over FY 2013
- **20,763 shares a day** on average since January 1, 2014

(100-point basis at 31.12.2011)



Shareholder' questions

Following the first implant in France, are you still looking at centers abroad to speed things up?

The international clinical program has been part of our strategic thought process since the beginning, and is a necessity given the global reach we aim to give to this project and the need to comply with best clinical practices. We would like to remind readers that the clinical trial consists of two phases: a feasibility study on 4 patients and, assuming this first phase is a success, a broader pivotal study on 20 to 25 patients. For the feasibility study, we feel more comfortable to call on the huge experience of the three French teams we have worked alongside for many years. In any case, we will then extend the pivotal study to hospitals in other countries, those that already indicated their support in May or other European hospitals that have shown significant interest in participating in our clinical development.

Why does CARMAT publish so little regarding its implants?

Beyond the unsolicited media coverage of the first implant, CARMAT follows a communication strategy regarding its clinical trials that is framed by its legal and regulatory obligations (Public Health Code, AMF regulations, Huriet Law, etc.), notably concerning the strict application of the contracts tying us to investigation centers, compliance with the independence of the boards of experts, the confidentiality of trials and the protection of patient data. The fact that the first patient has reached the required survival threshold, as reported in the media, cannot lead anyone to draw any conclusion on the trial success yet, and we therefore need to be cautious and have a duty of confidentiality. The interim or definitive results will only be published once we have received positive opinions from the study's independent analysis and monitoring boards, as well as from CARMAT's Scientific Advisory Board.

What is the cost of implanting a prosthesis within the framework of the clinical trial?

It is not possible to carry out a cost study during the clinical phase, insofar as it is not representative of a routine operation. Health economics data will be collected at a later time. Furthermore, as for heart transplants, the cost varies for each country, hospital or even patient. It depends on a number of factors, and notably the given timeframe before and after the implant. The cost of the time spent on the waiting list with repeated hospital admissions, for example, or the cost of treating a cancer of the lymphatic system resulting from immunosuppressor therapy. In the United States, a study estimates an average cost at $997,000 taking into account only the 30 days prior to and 180 days following the operation.

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Financial agenda

Wednesday February 12, 2014
2013 annual results

Wednesday April 2, 2014
Shareholders' General Meeting

Tuesday September 30, 2014*
2014 half-year results

** dates subject to change*

CARMAT in the media

LE FIGARO

January 21, 2014
"It has been a month since a first CARMAT artificial heart, developed by Professor Alain Carpentier, was implanted into a human patient [...] It seems obvious, but this is decisive insofar as it is a totally innovative heart that had never before been tested on a human being."

AFP

January 17, 2014
"Much applauded, Professor Alain Carpentier gave all sorts of technical details regarding his artificial heart at a landmark press conference late on Friday, at the end of which he received a standing ovation from the specialists attending the meeting."

PARIS MATCH

December 25, 2013
"They are the heroes of a saga that for a long time was considered to be nothing more than science fiction. On Wednesday December 18, at the Georges Pompidou European Hospital, an artificial heart was implanted in a man in his seventies who was suffering from terminal heart failure that would have left him little time to live."

Les Echos
Le Quotidien de l'Economie

December 23, 2013
"This could potentially concern almost 100,000 people with serious heart problems in Europe and the United States who are too old to have any chance of being given a heart transplant."

Le Monde

December 22, 2013
"This is a world first that had been eagerly awaited for years, and is a new stage in the great adventure being undertaken by the CARMAT French artificial heart, the first patent for which was registered by Professor Alain Carpentier 25 years ago. Since Wednesday December 18, a man is living with a totally artificial heart."

The Telegraph

December 21, 2013
"Unlike previous artificial hearts, created mainly for temporary use, the design by the French CARMAT biomedical firm is intended to replace a real heart for as many as five years."