Developing breakthrough pioneering therapies for life-threatening diseases

www.celyad.com
## Contents

Cancer and cancer treatment evolution .............................................................................................................. 4
Immunotherapy for cancer treatment ..................................................................................................................... 4
Chimeric antigen receptor T-cells (CAR T-cells) .................................................................................................. 4
Autologous and Allogeneic Approaches .............................................................................................................. 6
Current CAR-T products and indications .......................................................................................................... 7
Natural Killer Cells and the Innate Immunity ....................................................................................................... 7
Natural killer receptor CAR-T cell platform ....................................................................................................... 7
Differentiation and advantages of NKR-2 T-cells .............................................................................................. 8
In vivo animal studies with NKR-2 ..................................................................................................................... 8
Clinical development of NKR-2 ......................................................................................................................... 9
Celyad’s other developments of the platform .................................................................................................... 9
Our Immuno-Oncology Pipeline ....................................................................................................................... 9
Treating Heart Failure by engaging the heart’s reparative mechanisms ......................................................... 11
The Cardiopoiesis Platform: a fundamental research lead at Mayo Clinic .................................................... 13
C-Cure®: first-in-class cell-based therapy to treat heart failure ..................................................................... 13
C-CathezTM: unique intraventricular injection catheter ............................................................................... 14
C-Cure®: where the story begins .................................................................................................................... 16
CHART-1: from the 1st patient treated to a Phase III European trial ............................................................. 16
CHART-2 ......................................................................................................................................................... 17
Our Cardiology Pipeline ................................................................................................................................... 18
Glossary ............................................................................................................................................................ 18
Press contacts .................................................................................................................................................. 23
Celyad's program in immuno-oncology

Directing a weaponized attack on cancer with the NKR-T cell-based immunotherapy
Cancer and cancer treatment evolution

Cancer is one of the leading causes of death worldwide, accounting for over 8 million deaths in 2012. Cancer, known also as a malignant tumor, is a group of diseases that develops when normal cells in a particular part of the body begin to grow out of control. Cancer cells that arise in a specific organ, such as liver or lung, or body structure can potentially spread to other organs in a mechanism called metastasis. Cancer generally forms a solid tumor mass (such as lung or colon cancers). Some cancers like leukemia (blood cancer) or lymphoma (bone marrow cancer) do not form masses, and are called liquid tumors.

Cancer treatments in the last century have always been a balance between very active drugs with a lot of side effects, or less active drugs with lesser side effects. Indeed, the intent of those therapies was to kill cancer cells while avoiding the destruction of healthy cells. In the first half of the 20th century the therapeutic arsenal, alongside surgery in the case of solid tumors, included drugs killing dividing cells, and therefore preferentially active on cancer cells, and radiation focused on the tumor site.

Through better understanding of the cancer biology therapies have developed to become more targeted, and researchers are finding ways to minimize side effects.

Although cancer therapeutics have been and continue to be one of the most active areas in terms of drug development, there is still a lot of room for improvement. One of the current focus areas is immunotherapy, which makes use of the body’s own immune (defense) system to fight cancer. This is the field of cancer immunotherapy, or immune-oncology.

Immunotherapy for cancer treatment

Cancer cells produce abnormal proteins. The immune system typically recognizes these abnormal proteins which allow the highly efficient elimination of the cells that produce them in a process known as immune surveillance. Each of us develops cancer cells very often, but those cells do not turn into tumors because our immune system destroys them at early stages. Immunotherapy is based on the premise that our immune system is capable to destroy abnormal cells such as cancer cells, but in some instances, the cancer cells develop mechanisms that allow them to evade the detection or the activity of our immune defenses. The therapies developed in immune-oncology attempt to restore and to activate the immune system ability to detect and destroy cancers.

A growing understanding of cancer and of the immune system has led to remarkable progress in this field, which is profoundly changing treatment standards and expanding therapeutic options for cancer patients.

Chimeric antigen receptor T-cells (CAR T-cells)

A CAR-T cell is an immune construct that gathers a T lymphocyte, with a Chimeric Antigen Receptor, an intracellular signaling protein and a co-stimulatory molecule.

A central player in cancer immunotherapies is a type of white blood cell known as the T cell which is equipped with cell killing mechanisms (called cytotoxicity). In healthy subjects, T cells identify and kill infected or abnormal cells, including cancer cells.

A Chimeric Antigen Receptor (CAR) is engineered by inserting, in the DNA of a T-cell, a sequence that will push the T cell to express an antibody (immune defense) designed to recognize and bind an antigen (a protein identified as noxious by the immune system) present on the cancer cell. The trick here is to find an antigen that is expressed by a cancer cell and not by a normal cell.
To make this construction effective in killing cancer cells, another protein must be added inside the T-cell that will act as a signal that triggers cell killing once antibody/antigen binding has occurred. This intracellular signaling is usually a fragment of a protein called CD3. A T cell combining the antibody that allows the recognition of the cancer cell and the signaling that allows it to destroy is a **CAR-T cell**.

In an attempt to render that CAR-T cell more potent, researchers have added other proteins, called co-stimulatory molecules, which are in charge of helping CAR-T cells survive for a longer period of time (persistence) after they have been injected in the body, and/or push them to multiply. The most used co-stimulatory molecules are called CD 28 or 4-1-BB.

The antibody, the intracellular signaling domain and the co-stimulatory molecules are all proteins that are manufactured by the T cell itself, once the instructions for coding them have been inserted in the genome (DNA) of the T cell.

The CAR manufacturing technology modifies T cells outside the body. The steps are the following: (i) harvest cancer patient’s white blood cells from a normal blood draw in a process called leukapheresis, (ii) selection of the T cells from the white blood cells, (iii) transfer of the genes that code for the CAR in the DNA of the T Cells (iii) multiply the CAR to reach a therapeutic dose (iv) infuse these CAR-T cells back into the patient.
After administration of the CAR T-cells to the cancer patient, these cells pair with their target antigen on the cancer cells. This triggers further multiplication of the cells and activation of the cytotoxic (cell-killing) effect.

**Autologous and Allogeneic Approaches**

In autologous CAR-T-cell-based therapy, the T-cells to be engineered originate from the patient that will be treated. The big advantage being that the patient’s immune system does not reject the CAR-T cells obtained from their own T cells, nor do the injected T cell reject the patient normal tissues.

CAR-T-cell-based therapies are currently autologous, but researchers are working to find other approaches that would allow donor cells to be used (allogeneic).

The complexity of this approach lies in that T cells from the donor would be recognized as "foreign" by the patient that receives them and the patient immune system will be activated to reject these donor CAR-T cells. This reaction is called “Host versus Graft Disease” (HvGD).

In addition, as the injected cells are part of the donor immune system, they will also recognize the patient normal tissues as "foreign". The injected CAR-T cells will therefore reject or attack the patient normal tissues and induced a disease called the “Graft versus Host Disease” (GvHD). Those two reactions (GvHD and HvGD) render allogeneic therapies ineffective or even dangerous if performed without modifications.

The mechanism responsible for one part of the rejection (GvHD) is mostly driven by a protein naturally present at the surface of the T Cell called the T Cell Receptor (TCR). One approach to prevent GvHD is to silence this TCR on the donor cells. This can be done for by removing the gene that codes for the TCR in the T Cell that will be used (Gene Editing techniques), or by inserting a gene that codes for a fake non-functional TCR. This could reduce or eliminate the GvHD issue.

The HvGD however is much more complex to tackle than the GvHD. Indeed, the HvGD does not rely on just one protein (as it is the case for the GvHD which relies on the TCR), but on a complex web of signals (the MHC or Major Histocompatibility Complex) that cannot be inhibited simply.

This means that current “allogeneic” approaches, while representing a significant advance in terms of ease of use and simpler logistics, may still need to be “matched” between donors and patients.
recipients (patients), a little bit like blood transfusions are matched, at least for patients in which the immune system is functional. This matching would be done like in any organ transplantation through a Human Leukocyte Antigen (HLA) comparison between the donor and the patient. Current allogeneic approaches are not yet fully “off the shelf” solutions.

**Current CAR-T products and indications**

The most promising results of CAR-T cell therapies have been obtained in relapsed ALL. ALL stands for Acute Lymphoblastic Leukemia, a type of blood cell cancers originating from B cells. B cells or B lymphocytes are close cousins of T cells, and are another subset of white blood cells. The CAR-T that was used in this instance is bearing an antibody to the CD19 antigen, and the treatment achieved a complete remission in about 90% of patients that had failed all other therapies.

Normal B cells have a CD19 antigen on their surface, and, when the B cells become cancerous, they usually retain the expression of CD19. This means that CAR-T cells using CD19 as target, can recognize cancerous and normal B cells and kill them both.

CAR CD19 based therapies have therefore been used successfully in two relatively rare types of B cell malignancies, Acute Lymphoblastic Leukemia (ALL) and Chronic Lymphocytic Leukemia (CLL).

As CD19 is present on B cells, (healthy or sick), a treatment with a CD19 based CAR will eradicate both healthy and cancerous B cells, forcing the patient to receive immunoglobulins (proteins active in the immunity secreted by healthy B cells) during the remainder of his or her life.

**Natural Killer Cells and the Innate Immunity**

Natural Killer Cells (NK cells) are yet another type of white blood cells. They constitute the first line of defense against external aggression (viruses or bacteria) and against cancer. NK cells primary role seems to be surveillance, early detection and essentially to hold the line until T cells and other immune cells can come to the rescue.

NK cells are part of the innate immunity, meaning that they do not need to be activated or to be exposed to an aggression that created memory such as a prior infection (B and T cells need to be activated or rely on acquired memory). Hence NK cells are part of the innate immunity versus the acquired (or adaptative) immunity.

In order to recognize their targets, NK cells use receptors (proteins) present on their surface that recognize specific targets, called ligands, expressed by cells under stress. NK cells have both activating receptors, such as NKG2D, or NKp30, and inhibiting receptors.

NK cells will be activated if the balance between activating signals and inhibiting signals tilts in favor of the activating signals. The physiological purpose of that balance is to prevent NK cells from attacking healthy cells in our body and still be active against stressed cells. This balance, however, is also used by cancer cells to evade the body immune system. Some experimental therapies are attempting to interfere with the inhibitory signals of NK cells and unleash the NK cell killing activity unhampered by the inhibitory signals.

**Natural killer receptor CAR-T cell platform**

The Celyad T-cell immunotherapy approach is unique and builds on work conducted by Professor Charles Sentman and his team at Dartmouth College (Hanover, NH). Sentman had the idea of copying the NK activating receptors (for example NKG2D or NkP30) and insert them on a T cell

---

very much like other CAR approaches. Instead of inserting a gene that codes for an antibody (CD19 for example), Sentman inserted genes that coded for the NKG2D or the NkP30 receptors. Sentman used the same CD3 intracellular signaling construct as what is used in other CARs (a portion of the CD3 protein). Hence, a new CAR platform was invented, named NKR-T, meaning NK Receptor T cell.

NKR-T uses also a co-stimulatory domain to increase the potency of the cell, but instead of inserting a gene coding for CD28 or 4-1-BB like other CAR-T, NK receptor naturally use a co-stimulatory molecule already present in T-Cell, called DAP 10 making the overall CAR construct much simpler.

Differentiation and advantages of NKR-2 T-cells

What is unique about NKR-T is that contrary to the antibodies that are very specific to one antigen (in this case the CD19 antigen), and therefore to one type of cancers (in this case B cells based cancers), the receptor used can target many or most cancers. Indeed, in the example of NKG2D, the receptor binds to 8 different ligands (protein present on the target cells). Those ligands are generically expressed by cells that are suffering, such as cells that become cancer cells or become infected. Hence NKR-T is a new cell therapy platform that, contrary to other traditional CARs, can target not only one cancer, but the vast majority of cancers (i.e. blood cancers and solid tumors such as ovarian, lung, breast or colorectal amongst others).

In addition, preclinical studies results have demonstrated that NKG2D based CARs (NKR-2) is not only active against the tumor but also against its microenvironment since the abnormal blood vessels that feed the tumor as well as the inhibitory mechanisms that help the cancer cells evading the immune system, also express the ligands targeted by the NKG2D receptor.

In vivo animal studies with NKR-2

In multiple mouse models of blood and solid tumors, treatment with NKR-2 led to long-term tumor-free survival. In those experiments, it was shown that NKR-2 targets cancer cells and kills them, targets blood vessels that feed the tumor and destroys them, targets MDSCs and reduces the escape mechanisms of the tumor, and finally and quite uniquely creates a long term memory (not unlike a vaccination) against the tumor it destroyed.

A strong body of scientific evidences demonstrating the activity and the safety of NKR-2 were published in top peer reviewed scientific journals.
Clinical development of NKR-2

Autologous NKR-2 is currently being evaluated clinically in a first-in-human Phase I/IIa dose-escalation study (ClinicalTrials.gov NCT02203825) at the Dana-Farber Cancer Institute (Boston, MA), to assess safety and feasibility in relapsed or refractory Acute Myeloid Leukemia (AML) and Multiple Myeloma (MM) patients (two blood related cancers, together constituting more than 50% of all blood cancers). No safety issues have been observed so far and trial results are expected throughout 2016.

The therapeutic potential of this technology allows Celyad to plan for a large clinical program testing the activity of this compound in many different cancer indications.

Celyad’s other developments of the platform

Celyad acquired another receptor in the same NK receptor based CAR, using the NkP30 NK cell activating receptor. NkP30 is therefore very similar to NKG2D although using a different set of ligands. B7H6 is a more traditional antibody based CAR (using an antibody and not a receptor of NK cells), but it is the ligand of NKP30 and is present also on many different cancers.

Our Immuno-Oncology Pipeline

![Immuno-Oncology Pipeline](image)
Celyad's program in cardiovascular diseases

C-Cure®: first-in-class reparative therapy for heart failure treatment
Treating Heart Failure by engaging the heart’s reparative mechanisms

Cardiovascular diseases are the first cause of death in the world. Heart attacks and myocardial infarction may cause immediate death or a relatively high morbidity rate, considering the irreversible damage caused to the heart. The prevention and treatment of these diseases are thus a major issue and numerous clinical efforts are being made to improve the care and treatment of cardiac disorders.

See references below\textsuperscript{2,3,4,5,6,7}

According to the World Health Organization, in 2012, approximately 37% of all global deaths from non-communicable diseases were attributable to cardiovascular etiologies. Cardiac diseases can be broadly divided into diseases linked to impairment of blood flow to the heart muscle, or ischemic causes, and diseases linked to other causes, or non-ischemic causes, such as hypertension and metabolic disorders. If left untreated, cardiac diseases can lead to heart failure (HF).

\textsuperscript{3} Mozaffarian, a report from AHA, circulation 2016.
\textsuperscript{7} Lopez-Sendon J, "The Heart Failure Epidemic" Medicographia 2010.
What is Heart Failure?

Heart failure (HF) is a very serious condition in which the heart cannot pump enough blood to meet the body’s metabolic needs. As a natural evolution of most cardiac diseases, HF is very common, affecting 1% to 2% of the adult population in developed countries. Approximately 5.7 million patients were diagnosed with HF in the United States in 2012, according to the American Heart Association (AHA). The prevalence of HF is increasing due to an aging population and the increasing prevalence of major cardiovascular risk factors, such as obesity and diabetes. Population studies published in Nature Reviews Cardiology have estimated that one in five people over the age of 40 will develop HF during his or her lifetime. Despite the extensive use of effective drugs and devices, the long-term prognosis associated with heart failure is dire, with approximately 50% mortality at five years following initial diagnosis, according to a 2014 report from the American Heart Association. HF patients vary in their symptoms from very mild, through shortness of breath during moderate exercise, and then shortness of breath during light exercise. In the most severe stages, patients are exhausted even at rest.

What is ischemic heart failure?

The most frequent etiology of HF arises from the effects of coronary disease in damaging the left ventricle, leading to what is known as ischemic cardiomyopathy. The effects of one or more episodes of damage (myocardial infarction) will lead to the reduction of the left ventricular ejection fraction (LVEF), which is a measure of the percentage of blood leaving your heart each time it contracts. This process is often recurrent, resulting in a cumulative and invariably progressive deterioration of the heart function. It is estimated that 62% to 70% of advanced heart failure patients have an ischemic origin, 75% of them have a reduced left ventricular ejection fraction. According to existing statistics, it is this population of patients whose lives are most impacted by poor quality of life, frequent need of hospital care, in emergency admission for the majority of cases, and bear the highest risk of death.

Today HF cannot be cured or repaired, and most of the current therapies only reduce the severity of symptoms. Current drug therapies in particular have shown important effect in moderate heart failure patients but the vast majority of advanced heart failure patients are left without alternative than waiting for the disease to progress. Eventually, the younger ones may benefit from final therapeutic resorts such as cardiac transplantation and destination mechanical circulatory support, which are limited by donor heart availability, patient eligibility, and immunologic or other medical complications. While some medical devices (such as pacemakers and heart pumps) have improved the function of a damaged heart, no currently available heart failure treatment has demonstrated an ability to repair the scarred regions of a heart. As such, reparative therapies, that have the goal of rebuilding an organ that has become non-functional, when approved, would offer new hope to patients who otherwise have limited choices. Consequently, of all the causes of weakening of the heart muscle, ischemic cardiomyopathy appears to be the most likely to respond to reparative therapy.

---

8 Bursi F, Systolic and diastolic heart failure in the community. JAMA. 2006;296:2209–2216
The Cardiopoiesis Platform: a fundamental research lead at Mayo Clinic

Celyad is developing the breakthrough proprietary Cardiopoiesis platform, which is based on fundamental research and proprietary technology from the Mayo Clinic, a premium R&D and clinical institution in the US.

This novel platform is designed to drive the differentiation of multipotent stem cells into new cardiac progenitor cells, which are close to become cardiac stem cells.

While most organs (such as the skin and bone) have a greater or lesser capacity for self-repair of damage, the heart does not have this capacity: it does not harbour large quantities of cardiac stem cells (CSCs) that can be used for self-repair, CSCs that are present in the heart are in a dormant state.

Fundamental research at Mayo Clinic uncovered the mechanisms in the embryo that make an embryonic stem cell become a heart cell. This led to the identification of a ‘cardiopoietic’ combination of proteins signaling the transformation of generic adult stem cells from other tissues into cardiac progenitor cells.

The Cardiopoiesis platform aims to replicate the normal processes of cardiac development in the embryo, without attempting to permanently or temporarily modify the genome of the cell. As such, the platform recapitulates what nature does, while at the same time turning on every patient’s reparative potential. The platform is also highly versatile and could be applied to various stem cell sources.

This platform represents one of the main promise of Regenerative medicine, which is one of the current research strategies for reducing dysfunction of organs, such as the heart for example. 11

C-Cure®: first-in-class cell-based therapy to treat heart failure.

C-Cure® is Celyad’s most advanced product candidate based on the Cardiopoiesis platform and is being developed for HF indications. It is called as autologous therapy, as it is based on the patient’s own cells, which are harvested from his bone marrow, treated with the cardiopoietic growth factors and then re-injected into his heart. It is designed to produce new heart muscle cells which behave identically to those lost in infarction without carrying the risk of rejection.

---

10 Sherman, Cellular Therapy for Chronic Myocardial Disease: Nonsurgical approaches, Basic Appl. Myol. 13(1) 11-14.
1. Bone marrow is drawn from the patient
2. Stem cells are selected and expanded
3. Cells are guided towards cardiac differentiation with a set of proprietary growth factors of Celyad. They become cardiac progenitor (cardiopoietic cells)
4. Cardiac progenitor cells are injected back into the heart using C-Cathez™ and terminally differentiate
5. Cardiac regeneration

C-Cure® has two modes of action:

- Directly through the proliferation, engraftment and terminal differentiation of the injected cells.
- Indirectly through the beneficial effect of the factors excreted by the transplanted cells on the host’s own resident cardiac stem cells through a so called “paracrine effect” that results in the revascularization of the muscle and the recruitment of resident cells.

C-Cathez™: unique intraventricular injection catheter.

This new therapy involves the injection of cells directly into the heart through a device. One of the limitations of the existing injection techniques was the low rate of retention of the therapeutic solutions injected into the organ, due to its porosity. In the case of the heart muscle, this rate of retention varies but does not exceed 5 to 10% depending on the injection methods used.\(^\text{12}\) This low rate of retention thus implies a non-optimal efficiency of these therapeutic solutions.

Therapeutic solutions are generally administered with the help of medical devices such as injection catheters, for example, whose configuration directly affects the efficiency and the

---

\(^{12}\) Bartunek et al., Delivery of Biologics in Cardiovascular Regenerative Medicine, Clinical Pharmacology & Therapeutic, 2009.
quality of the injection.\textsuperscript{13} Within the framework of an endocardiac injection, the risk of perforation of the heart muscle is accentuated because such a complication may lead to the patient’s death.

Celyad has developed a proprietary technology aimed at maximizing the delivery efficiency of regenerative therapeutics to the heart: C-Cath\textsubscript{ez}TM

\textbf{C-Cath\textsubscript{ez}TM Injection Catheter Included Items}

- C-Cath\textsubscript{ez}TM is an intra-myocardial delivery catheter, designed to reduce risk of myocardium perforation, increase needle stability and deliver enhanced fluid dynamics to improve retention.
- C-Cath\textsubscript{ez}C-Cath\textsubscript{ez}TM obtained CE mark in April 2012 and is therefore available for clinical use worldwide and commercial use outside of the U.S.

\textsuperscript{12} Heldman et al., Cell Therapy for myocardial infarction: Special delivery, Journal of Molecular and Cellular Cardiology, 44, 473-476.
C-Cure®: where the story begins...

In 2000, fundamental research was being conducted at Mayo Clinic (Rochester, Minnesota, USA) to unveil the mechanisms that make a stem cell differentiate into a heart cell. Prof. André Terzic and Dr. Atta Behfar head the research. At that time, in Belgium, a team of cardiologists from the Cardiovascular Center Aalst in Belgium, led by Prof. William Wijns, was working on a new cell therapy aimed to restore damaged heart muscle and to offer another alternative to graft. It is important to know that natural reparative mechanisms of the body are not able to fully regenerate damaged heart tissue. So, the researchers focused on using stem cells they would first convert into cardiac progenitor cells to then administer them directly around the tissues that were damaged after the infarction and that are causing heart failure.

As the specialists in Aalst (Belgium) did not have the capabilities to program stem cells into cardiac progenitor cells, they met a research team of Harvard (in Boston, Massachusetts) who had developed a specific method to do so. This was not the first time that a research team tried to develop a cell therapy to repair the heart but it was the first time that stem cells were converted into cardiac progenitor cells that were able to repair the tissue but also and overall to restore its contractile capacity. While the two teams were fostering their collaboration, the Mayo Clinic (Rochester, New Hampshire) joined the project.

In 2004, Cardio 3 SA (the Company’s predecessor entity), was created by Michel Lussier, Christian Homsy and William Wijns to leverage research collaboration between Mayo Clinic and Cardiovascular Center Aalst in Belgium. The Company started to develop its expertise in cell therapy engineering. In 2007, Cardio 3 SA became Cardio 3 BioSciences and entered a license agreement with Mayo Clinic to further develop the cardiopoiesis platform and work on a future cell-based therapy for the treatment of ischemic heart failure: C-Cure®.

As the research performed at Mayo Clinic had let to a number of high level-publications in peer-review journals, the results obtained allowed Cardio 3 BioSciences to enter immediately into the last phase of preclinical studies before performing first clinical testing in human.

CHART-1: from the 1st patient treated to a Phase III European trial

In 2009, Cardio 3 BioSciences treated the first patient participating in its Phase II/III clinical study to assess the safety and efficacy of C-Cure® beyond optimal clinical care in patients with heart failure. By the end of the year, 45 patients were enrolled in the study allowing to Cardio 3 BioSciences to complete the enrolment of its first stage pivotal trial. At that time, the study was being conducted in centers in Belgium and in Serbia.

In 2010, the Company reported first positive safety data as well as preliminary efficacy results from its clinical trial. After a three-month safety follow-up, the data were already demonstrating meaningful differences in ventricular size, ejection fraction and other measures of heart muscle activity in C-Cure® treated patients when compared to control and to baseline. At that time, the primary endpoint of the trial was left ventricular ejection fraction (a measure of how well the heart is pumping blood) at six months post treatment.
At the six-month follow-up point, the Phase II trial showed positive results, including significant functional and clinical benefit: patients that were treated with C-Cure® saw an 18.1% relative increase in left ventricular ejection fraction (LVEF) over baseline, while the mean LVEF increased only by 3.6% in patients enrolled in the control group. The trial also generated data that suggest favorable and statistically significant remodeling of heart muscle and improved heart muscle performance in the treatment versus control group. Signs of functional improvement were supported by improved fitness, shown by a significant mean difference in the 6-minute walking distance test between the treatment and control groups. Last but not least, the bone marrow of 70% of the attempted 30 patients was successfully processed into C-Cure®. CHART-1 Phase II results were published in the Journal of the American College of Cardiology (JACC)\textsuperscript{14}.

In 2012, Cardio 3 BioSciences received authorization from the Belgian Federal Agency for Medicines and Health Products (FAMHP) to begin its Congestive Heart failure Cardiopoietic Regenerative Therapy (CHART-1) European Phase III trial in Belgium. This represented a world premiere for a regenerative medicine product (more precisely an autologous stem cell therapy) targeting heart failure to be tested in the context of a Phase III trial.

This Phase III trial, that was aimed to recruit 271 patients in 12 countries in Europe, was designed as a prospective, multi-center, randomized, sham-controlled, patient-and-evaluator-blinded study comparing C-Cure® to a sham treatment. At that stage, the primary endpoint of the trial was defined as a composite endpoint including all the dimensions of the potential impact of the therapy: mortality and morbidity (clinical endpoint), quality of life questionnaire and Six Minute Walk Test (cardiac function endpoint), left ventricular structure and function at 9 months post-procedure (functional endpoints induced by the cell therapy)\textsuperscript{15}. In June 2013, the first patient of the Phase III trial was treated. The Phase III trial was also the first one using Cardio 3 BioSciences’ proprietary injection catheter C-Cathet\textsuperscript{TM} to administer C-Cure® to the patients.

In 2015, Cardio 3 BioSciences became Celyad. The Company completed the injection procedure for the last patient enrolled in CHART-1 Phase III trial, following the positive outcome of the futility analysis that was previously performed on a subset of patient data. This achievement made of C-Cure® not only the most advanced product candidate of Celyad but also the most advanced cardiopoietic cell-based therapy ever to be developed for the treatment of ischemic heart failure. With the first results of the CHART-1 European Phase III trial, with such an advanced trial, Celyad is one of the global leaders in the field of regenerative medicine.

**CHART-2**

The main objective of this second phase III trial is to obtain a market authorization in other parts of the world such as the US, Asia and Latin America. Though the protocol was discussed with the FDA, Celyad made the decision to wait for the CHART-1 result before starting the patient recruitment.


\textsuperscript{15} Bartunek & al, Congestive Heart Failure Cardiopoietic Regenerative Therapy (CHART-1) Clinical trial, EJHF 2015
Our Cardiology Pipeline

<table>
<thead>
<tr>
<th>Cardiology</th>
<th>Discovery</th>
<th>Pre-Clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-CURE: Ischemic Heart Failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHART-1 (EU)</td>
<td></td>
<td></td>
<td>Ph III completed. Full data to be presented August 28th at ESC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHART-2 (US)</td>
<td></td>
<td></td>
<td>Ph II completed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Glossary

A

**Acute Myocardial Infarction (AMI)** - Commonly known as a heart attack, is the interruption of blood supply to part of the heart, causing some heart cells to die. This is most commonly due to occlusion (blockage) of a coronary artery following the rupture of a vulnerable atherosclerotic plaque, which is an unstable collection of lipids (like cholesterol) and white blood cells (especially macrophages) in the wall of an artery. The resulting ischemia (restriction in blood supply) and oxygen shortage, if left untreated for a sufficient period of time, can cause damage or death (infarction) of heart muscle tissue (myocardium).

**Acute Myeloid Leukemia (AML)** - AML is a type of cancer that affects the blood and bone marrow. It is characterized by an overproduction of certain immature white blood cells, called myeloblasts or leukemic blasts.

**Allogeneic** - A situation in which the donor and the recipient are not the same person.

**Antibody** - Also known as an immunoglobulin is a protein produced mainly by plasma cells that is used by the immune system to identify and neutralize pathogens such as bacteria and viruses.

**Antigen** - Any substance that causes an immune system to produce antibodies against it.

**Autologous** - A situation in which the donor and the recipient are the same person.

C

**CAR T-Cell** - A CAR-T cell is a T lymphocyte (a type of white blood cells) in which a DNA construct, coding for a receptor, has been introduced artificially. The result of this engineered cell is that the T lymphocyte express the CAR (Chimeric Antigen Receptor) on its surface and is able to recognize a specific target through new engrafted receptor.

**Cardiac Progenitor Cells (CPCs)** - A cardioprogenitor cell is a cellular phenotype with the capacity to yield myocardial tissue and blood vessels upon differentiation.

**Cardiac Resynchronisation therapy (CRT)** - A CRT is a type of pacemaker (is a medical device which uses electrical impulses, delivered by electrodes contacting the heart muscles, to regulate the beating of the heart) that can pace both the septal and lateral walls of the left ventricle.

**Cardiac Stem Cells (CSCs)** - Cells that can give rise to all of the major cell types in the human heart.

**Cardiogenesis** - Development of the heart in the embryo.
Cardiogenic factors - A mixture of growth factors, cytokines and small molecules that have the capacity to drive Cardiopoiesis.

Cardiopoiesis - Process to drive stem cells towards the cardiac lineage.

Cardiopoietic Cells (CPCs) - Cells that are precursors of fully differentiated cardiac muscle cells. In the lab, CPCs can be generated from stem cells by culture in the presence of a specific cocktail of cardiotrophic factors discovered at the Mayo Clinic.

Cardiovascular Disease (CVD) - A group of disorders of the heart and blood vessels which includes:

- Coronary heart disease
- Cerebrovascular disease
- Peripheral arterial disease
- Rheumatic heart disease
- Congenital heart disease
- Deep vein thrombosis and pulmonary embolism

Consistency lots - Lots produced to documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to manufacture a product meeting its predetermined specifications and quality attributes.

Coronary Artery Disease (CAD) - A condition in which atherosclerotic plaque builds up inside the coronary arteries. Plaque is made up of fat, cholesterol, calcium and other substances found in the blood. This can cause angina (chest pain or discomfort) or a heart attack (when the blood flow to an area of the heart muscle is completely blocked, preventing oxygen-rich blood from reaching that area and causing it to die).

Co-stimulatory molecules - During the activation of lymphocytes, co-stimulation is often crucial to the development of an effective immune response. Co-stimulation is required in addition to the antigen-specific signal from their antigen receptors.

Cryopreservation - Cryopreservation is a process where cells or whole tissues are preserved by cooling to low sub-zero temperatures. At these low temperatures, any biological activity, including the biochemical reactions that would lead to cell death, is effectively stopped.

Embryonic Stem Cells (ESCs) - Stem cells derived from the undifferentiated inner mass cells of a human embryo. Embryonic stem cells are pluripotent, meaning they are able to grow (i.e. differentiate) into all derivatives of the three primary germ layers: ectoderm, endoderm and mesoderm.

Formulation - Formulation is the vehicle and the form in which an active compound is delivered in the body. Formulation is the vehicle and the form in which an active compound is delivered in the body.

Functional Assessment - The capacity of the patient to perform exercise.

Good Manufacturing Practices (GMP) - GMP is part of a quality system covering the manufacture and testing of active pharmaceutical products. GMPs are guidelines that outline the aspects of production and testing that can impact the quality of a product.
**Graft versus Host disease GvHD** - GvHD is a medical complication following the receipt of transplanted tissue from a genetically different person. GvHD is commonly associated with stem cell or bone marrow transplant but the term also applies to other forms of tissue graft. Immune cells (white blood cells) in the donated tissue (the graft) recognize the recipient (the host) as “foreign.” The transplanted immune cells then attack the host’s body cells.

**Heart Failure (HF)** - Heart Failure is a condition in which the heart has been damaged and cannot pump enough blood to meet the body’s metabolic needs. HF can be of ischemic or non-ischemic origin:

- Ischemic Origin (Coronary Artery Disease)
- Non-ischemic Origin
- Hypertension: high blood pressure;
- Other conditions such as heart valve disease, congenital heart defect, endocarditis (infection of the heart valves) and/or myocarditis (infection of the heart muscle).

The failing heart keeps working but not as efficiently as it should. HF patients cannot exercise because they become short of breath and tired. In the most severe forms, even slight exercises like walking a short distance are impossible.

**Human MSCs** - MSCs (see definition below) of human origin.

**Immunodeficient rodents** - A lineage of rodents (like rats or mice) that are genetically lacking some components of the immune system (the system that protects against external aggressions like infections).

**Implantable Cardioverter Defibrillator (ICD)** - Small battery-powered electrical impulse generator which is implanted in patients who are at risk of sudden cardiac death due to ventricular fibrillation and ventricular tachycardia.

*In vitro* (experiment) - Experiments done outside animal living systems.

*In vivo* (experiments) - Experiments done in animal living systems.

**Induced Pluripotent Stems Cells (IPS)** - IPSs are pluripotent cells derived from differentiated cells by forcing the expression of key pluripotency genes.

**Left Ventricular Assist Device (LVAD)** - A LVAD is a mechanical circulatory device that is used to partially or completely replace the function of a failing heart.

**Left Ventricular Ejection Fraction (LVEF)** - The fraction of blood pumped out of the left ventricle with each heartbeat.

**Ligand** - A ligand is molecule, as an antibody, hormone, or drug, that binds to a receptor

**Mesenchymal Stem Cells (MSCs)** - Cells located in many tissues serving to repair the organs and tissues. These cells are found in organs like bone marrow, adipose tissue, liver, and pancreas.
Multiple Myeloma (MM) - MM is a cancer of plasma cells. Plasma cells are mature B lymphocytes, a type of white blood cell, that help to fight infection by producing special proteins called antibodies or immunoglobulins. In myeloma, large numbers of abnormal plasma cells called myeloma cells are made in the bone marrow.

Multipotent Stem Cells - Cells that have the potential to give rise to cells from multiple, but a limited number of lineages; i.e. multipotent stem cells can differentiate into a number of cells, but only those of a closely related family of cells.

NK cell or Natural Killer cell - NK cells are lymphocytes of the innate immune system, which can eliminate targets directly and destroy cells (e.g. upon viral infection, or tumor cells)

Neovasculogenesis - Development of new blood vessels.

Paracrine - Paracrine signalling is a form of cell signalling in which the target cell is near ("para" = near) the signal-releasing cell.

Proteomics analysis - Proteomics is the large-scale study of proteins, particularly their structures and functions.

ScFv - ScFv stands for Single Chain variable fragment. It is not a fragment of an antibody, but instead a fusion protein of the variable regions of the heavy and light chains of antibodies.

Secretome - Term used to describe the set of proteins secreted by a cell, a tissue or an organism.

Sham - A "mock" treatment intended to ensure that patients do not know in which treatment arm of the clinical study they are. Intended to ensure that the study is unbiased by a potential placebo effect.

Stem cells - Stem cells are primal cells. They retain the ability to renew themselves through division and can differentiate into a diverse range of specialised cell types. Stem cells can be found in adult tissues (adult stem cells), embryos (embryonic stem cells or ESCs) or umbilical cord blood.

Systolic dysfunction - Impairment of the contractile function of the heart.

T Lymphocyte (also called T-cell) - A type of lymphocyte (a subtype of white blood cell) that play a central role in cell-mediated immunity.

TCR - TCR is a molecule found on the surface of T lymphocytes (or T cells) that is responsible for recognizing antigens bound to major histocompatibility complex (MHC) molecules.

Validated Test - A test that has been standardized and undergone rigorous evaluation and is now used as a standard by the industry and regulators.

Ventricular fibrillation (VF) - Ventricular fibrillation is a condition in which there is uncoordinated contraction of the cardiac muscle of the ventricles in the heart.
Ventricular Tachycardia (VT) – Sustained VT (SVT) - A ventricular tachycardia is a tachycardia, or fast heart rhythm, that originates in one of the ventricles of the heart.

- If the fast rhythm self-terminates within 30 seconds, it is considered a non-sustained ventricular tachycardia;
- If the rhythm lasts more than 30 seconds, it is known as a sustained ventricular tachycardia.
About Celyad

Founded in 2007, and based in Belgium, Celyad is a leader in engineered cell therapy with clinical programs initially targeting indications in cardiology and oncology. Celyad is developing its lead cardiovascular disease product candidate, C-Cure®, for the treatment of ischemic heart failure, and has completed enrollment of a Phase III trial in Europe and Israel. In addition, the Company is developing a next generation portfolio of CAR T-cell therapies that utilize human Natural Killer cell receptors for the treatment of numerous blood and solid cancers. Its lead oncology product candidate, NKR-2 (NKG2D CAR T-cell), entered a Phase I clinical trial in April 2015. Celyad’s ordinary shares are listed on Euronext Brussels and Euronext Paris under the ticker symbol CYAD and Celyad’s American Depositary Shares are listed on the NASDAQ Global Market under the ticker symbol CYAD.

To learn more about Celyad, please visit www.celyad.com

Forward looking statements

In addition to historical facts or statements of current condition, this press release contains forward-looking statements, including statements about the potential safety and feasibility of NKR-2-cell therapy and C-Cure and the clinical potential of the Company’s technology platform generally and the timing of future clinical trials, which reflect our current expectations and projections about future events, and involve certain known and unknown risks, uncertainties and assumptions that could cause actual results or events to differ materially from those expressed or implied by the forward-looking statements.

In particular, it should be noted that the safety data described in the release are preliminary in nature and the Phase 1 trial is not completed. There is limited data concerning safety and feasibility of NKR-2. These data may not continue for these subjects or be repeated or observed in ongoing or future studies involving our NKR-2 therapy, C-Cure or other product candidates. It is possible that safety issues or adverse events may arise in the future. These forward-looking statements are further qualified by important factors, which could cause actual results to differ materially from those in the forward-looking statements, including risks associated with conducting clinical trials; the risk that safety, bioactivity, feasibility and/or efficacy demonstrated in earlier clinical or pre-clinical studies may not be replicated in subsequent studies; risks associated with the timely submission and approval of anticipated regulatory filings; the successful initiation and completion of clinical trials, including Phase III clinical trials for C-Cure® and Phase I clinical trial for NKR-2; risks associated with the satisfaction of regulatory and other requirements; risks associated with the actions of regulatory bodies and other governmental authorities; risks associated with obtaining, maintaining and protecting intellectual property, our ability to enforce our patents against infringers and defend our patent portfolio against challenges from third parties; risks associated with competition from others developing products for similar uses; risks associated with our ability to manage operating expenses; and risks associated with our ability to obtain additional funding to support our business activities and establish and maintain strategic business alliances and business initiatives. A further list and description of these risks, uncertainties and other risks can be found in the Company’s Securities
and Exchange Commission filings and reports, including in the Company’s prospectus filed with the SEC on June 19, 2015 and future filings and reports by the Company. Given these uncertainties, the reader is advised not to place any undue reliance on such forward-looking statements. These forward-looking statements speak only as of the date of publication of this document. The Company expressly disclaims any obligation to update any such forward-looking statements in this document to reflect any change in its expectations with regard thereto or any change in events, conditions or circumstances on which any such statement is based, unless required by law or regulation. C3BS-CQR-1, C-Cure, NKG2D CAR T-cell, NKR-2, OnCyte, Celyad, Celyad, C-CathTM, CHART-1, CHART-2 and OnCyte logos are signs internationally protected under applicable Intellectual Property Laws. Mayo Clinic holds equity in Celyad as a result of intellectual property licensed to the Company.