

## TiGenix announces the clinical development of Cx611 in early rheumatoid arthritis and severe sepsis

**Leuven, Belgium – 30 June, 2014** – TiGenix NV (Euronext Brussels: TIG), the European leader in cell therapy, announced today that it will develop its intravenous-administered allogeneic stem cell product, Cx611, for patients suffering from early rheumatoid arthritis and for patients suffering from severe sepsis, a potentially life-threatening complication of infection.

“Having considered the demonstrated therapeutic effects of allogeneic stem cells, the animal and clinical data for Cx611 collected so far, the potential applications into areas of high unmet medical need, and the advice from clinical experts in Europe and in the United States, we are convinced that it is in early rheumatoid arthritis and in severe sepsis that we should concentrate our resources for Cx611” said Eduardo Bravo, CEO of TiGenix. “In early rheumatoid arthritis, Cx611 could offer patients a therapy with an alternative mechanism of action that delays the need to progress to biological drugs. In severe sepsis, Cx611 could be a therapy with a mechanism of action that provides significant advantages when combined with normal standards of care, delivering faster recovery and improved survival rates. Success in any of these indications would represent a major medical and commercial opportunity for Cx611.”

### Early rheumatoid arthritis

Rheumatoid arthritis is a chronic polyarticular inflammatory joint disease typically involving the small joints of the hands and feet that affects between 0.5 and 1% of adults in the developed world. Between 5 and 50 per 100,000 people develop the condition each year. After initial treatment with methotrexate and non-steroidal anti-inflammatory drugs (NSAIDs), and/or corticosteroids, disease activity in a number of patients is insufficiently controlled and typically leads to treatment with a group of drugs known as ‘biologicals’, such as the TNF-alpha inhibitors. Nevertheless, lack of an adequate response in a significant portion of treated patients, safety concerns, and declining efficacy over time, requiring a substantial number of patients to periodically change drugs, indicate the need for additional therapeutic approaches.

“There is a need for a treatment with an alternative mechanism of action that could increase the proportion of patients brought into remission and reduce the need to progress to chronic, sequential and expensive biological therapies”, said Frank Luyten, Professor and Chairman of Rheumatology, University Hospital of Leuven, Belgium.

In animal models, expanded Adipose-derived Stem Cells (eASCs) have been shown to down-regulate pro-inflammatory cytokines and up-regulate regulatory T cells which modulate the immune system. In a Phase IIa study of Cx611 in refractory rheumatoid arthritis completed and presented in 2013, the safety of the product was confirmed and signs of efficacy were encouraging. Some patients treated with Cx611 entered remission after years of treatment with conventional and biological drugs.

Assisted by a Steering Committee consisting of Professor Mark Genovese (Professor Immunology and Rheumatology, Stanford University, US), Professor Paul Emery (Professor of Rheumatology, University of Leeds, UK) and Professor José María Alvaro-Gracia (Head of the Biological Therapies Unit at the Hospital Universitario de La Princesa, Madrid, Spain), the principal investigator in the earlier Phase IIa study of Cx611 in refractory rheumatoid arthritis, TiGenix is working with a group of leading clinical experts, including Professor Luyten

(Belgium), to complete the protocol for a randomised, double-blind, comparative Phase II study to test the efficacy of Cx611 in patients exhibiting substantial disease activity of rheumatoid arthritis despite treatment with methotrexate and corticosteroids, but unexposed to a biological drug. Recruitment for the proposed study could start in the third quarter of 2015 and TiGenix would expect final results to be available by the first half of 2017.

## **Severe Sepsis**

Sepsis is a potentially life-threatening complication of infection. Sepsis occurs when inflammatory molecules released into the bloodstream to fight the infection trigger systemic inflammation. This inflammation can trigger a cascade of detrimental changes that damage multiple organ systems, causing them to fail. If sepsis progresses to septic shock, blood pressure drops dramatically, which may lead to death. People with severe sepsis require close monitoring and treatment in a hospital intensive care unit. Drug therapy is likely to include broad-spectrum antibiotics, corticosteroids, vasopressor drugs to increase blood pressure, as well as oxygen and large amounts of intravenous fluids. Supportive therapy may be needed to stabilise breathing and heart function and to replace kidney function.

“Even today, patients with severe sepsis have a low survival rate so there is a critical need to improve the effectiveness of current therapy,” said Professor Pierre-François Laterre, Professor of Medicine and Head of Intensive Care, Saint Luc University Hospital, Brussels, Belgium. “Only a small number of new molecular entities are currently in development for severe sepsis. Based on the available data, I believe there is a strong rationale to study Cx611 in this patient population.”

In animal models, eASCs have been shown both to decrease pro-inflammatory mediators and increase anti-inflammatory mediators, and to have anti-microbial effects. As a result of this mechanism of action, Cx611 has demonstrated efficacy in significantly reducing mortality in two animal models of sepsis. TiGenix therefore believes that Cx611 has a potentially important role when combined with current standards of care in patients with severe sepsis.

The company is working on the development plan of Cx611 in this indication with an Advisory Board of Professor Pierre-François Laterre, Dr. Bruno François (Service de Réanimation Polyvalente, Centre Hospitalier Universitaire, Limoges, France), Professor Sébastien Gibot (Service de Réanimation Médicale, Centre Hospitalier Universitaire, Nancy, France) and Professor Tom van der Poll (Department of Internal Medicine, Academic Medical Center, University of Amsterdam, The Netherlands). As well as additional animal model testing, TiGenix will start a randomised, placebo-controlled trial to test the mechanism of action of Cx611 in healthy volunteers challenged with a bacterial endotoxin (lipopolysaccharide), a potent pro-inflammatory constituent of the outer membrane of Gram-negative bacteria, which elicits a strong inflammatory response inducing sepsis-like clinical symptoms. TiGenix expects to complete this study by the third quarter of 2015 and follow up with a phase II trial of Cx611 as an add-on therapy to the standard of care in patients with severe sepsis.

## Conference call webcast

On Monday, 30 June, at 15:00h CEST/9.00am EDT, TiGenix will conduct a conference call webcast. The following speakers will present more details on the development plan for Cx611 and will take questions.

- Eduardo Bravo, Chief Executive Officer, TiGenix
- Wilfried Dalemans, Chief Technical Officer, TiGenix
- Dr Frank Luyten, Professor and Chairman of Rheumatology, University Hospital of Leuven, Belgium
- Dr Pierre-Francois Laterre, Professor of Medicine and Head of Intensive Care, Saint Luc University Hospital, Brussels, Belgium

Please dial one of the following numbers to participate:

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+1 416 216 4141	Canada
+33 1 76 77 22 26	France
+31 20 716 8256	Netherlands
+34 91 114 6582	Spain
+46 8 5033 6538	Sweden
+44 20 3427 0503	UK
+1 212 444 0481	USA

Confirmation code: 2890120

The webcast can be followed live online via the link:

<http://www.media-server.com/m/p/zid4ym8b>

The press release and the slide presentation will be made available in the Newsroom/Events section of the TiGenix website. A replay of the webcast will be available on the website shortly after the conference call.

## For more information

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## About Cx611

*Cx611 is an intravenously-administered product of allogeneic expanded adipose-derived stem cells.*

*In 2013, TiGenix reported positive 6-month safety data from its Phase IIa study of Cx611 in refractory rheumatoid arthritis, as well as a first indication of therapeutic activity using standard outcome measures and biologic markers of inflammation for at least three months after dosing.*

*The multicenter, randomised, double-blind, placebo-controlled Phase IIa trial enrolled 53 patients with active refractory rheumatoid arthritis (mean time since diagnosis 15 years), under treatment with at least one non-biologic disease-modifying anti-rheumatic drug (DMARD), who failed to respond to at least two biologic drugs (mean previous treatment: 3 or more DMARDs and 3 or more biologic drugs). The study design was based on a three-cohort dose-escalating protocol. For both the low and medium dose regimens, 20 patients received active treatment versus 3 patients on placebo; for the high dose regimen, 6 patients received active treatment versus 1 on placebo. Patients were dosed at*

Days 1, 8, and 15 and were followed up monthly over a six-month period. Follow-up consisted of a detailed monthly work-up of all patients, measuring all pre-defined parameters. The aim was to evaluate the safety, tolerability and optimal dosing over the full 6 months of the trial, as well as exploring therapeutic activity.

Only one patient suffered serious adverse events that led to a discontinuation of treatment. All other side effects were mild and transient indicating that eASCs are well tolerated and associated with an overall acceptable safety profile.

Measured clinical activity scores were ACR20<sup>2</sup>, ACR50<sup>2</sup>, ACR70<sup>2</sup>, EULAR<sup>3</sup> response rates, and the disease activity score, DAS28<sup>4</sup>. To gain a first insight into therapeutic activity, these parameters were evaluated every month for six months. Indeed, patients receiving Cx611 had higher ACR scores, better EULAR response, and higher DAS28 scores than patients receiving placebo over three months and a sustained benefit over six months.

<sup>2</sup> ACR 20 means a 20% improvement in tender or swollen joint counts as well as 20% improvement in at least three of the following five criteria: patient assessment, physician assessment, erythrocyte sedimentation rate, pain scale and functional questionnaire. The ACR50 and ACR70 categories adhere to the same criteria, but for 50% and 70% improvement, respectively.

<sup>3</sup> EULAR, European League Against Rheumatism

<sup>4</sup> DAS28, Disease Activity Score 28 joint count

## **About TiGenix**

TiGenix NV (Euronext Brussels: TIG) is a leading European cell therapy company with a pipeline of clinical stage allogeneic adult stem cell programmes for the treatment of autoimmune and inflammatory diseases and a marketed product for cartilage repair, ChondroCelect. TiGenix is headquartered in Leuven (Belgium) and has operations in Madrid (Spain). For more information, please visit [www.tigenix.com](http://www.tigenix.com).

## **Forward-looking information**

This document may contain forward-looking statements and estimates with respect to the anticipated future performance of TiGenix and the market in which it operates. Certain of these statements, forecasts and estimates can be recognised by the use of words such as, without limitation, “believes”, “anticipates”, “expects”, “intends”, “plans”, “seeks”, “estimates”, “may”, “will” and “continue” and similar expressions. They include all matters that are not historical facts. Such statements, forecasts and estimates are based on various assumptions and assessments of known and unknown risks, uncertainties and other factors, which were deemed reasonable when made but may or may not prove to be correct. Actual events are difficult to predict and may depend upon factors that are beyond the Company's control. Therefore, actual results, the financial condition, performance or achievements of TiGenix, or industry results, may turn out to be materially different from any future results, performance or achievements expressed or implied by such statements, forecasts and estimates. Given these uncertainties, no representations are made as to the accuracy or fairness of such forward-looking statements, forecasts and estimates. Furthermore, forward-looking statements, forecasts and estimates only speak as of the date of the publication of this document. TiGenix disclaims any obligation to update any such forward-looking statement, forecast or estimates to reflect any change in the Company's expectations with regard thereto, or any change in events, conditions or circumstances on which any such statement, forecast or estimate is based, except to the extent required by Belgian law.