



In addition, severity of perianal Crohn's disease was assessed at baseline and all study visits with the Perianal Disease Activity Index (PDAI). In the mITT population, the PDAI score was similar in the Cx601 and the placebo groups at baseline. The improvement in PDAI with Cx601 was significantly greater than placebo at week 6, 12 and 18. In addition, the mean total PDAI score at week 24 with Cx601 (4.4) was close to the threshold for inactive perianal disease (PDAI<4) at which patients do not need medical or surgical treatment.

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract that affects approximately five million patients worldwide.<sup>4</sup> People living with Crohn's disease often experience complex perianal fistulas for which there are limited treatment options. Recognizing the debilitating nature of the disorder and the lack of treatment options, in 2009 the European Commission granted Cx601 orphan designation for the treatment of complex perianal fistulas in Crohn's disease. In March 2016, TiGenix announced that it submitted the Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) for Cx601. TiGenix also recently announced 52-week data<sup>5</sup> indicating the potential for efficacy and safety of a single treatment of Cx601 are maintained during a year of follow up.

"We are very proud of the results of this study," said Prof. Dr. JuliÀn PanÀs, ADMIRE-CD Global Study Coordinator and Head of the Inflammatory Bowel Diseases Unit at the Hospital ClÀnic of Barcelona. "The Lancet is one of the most highly regarded and well known medical journals in the world; we are very delighted to have the Cx601 data selected by this prestigious publication," he continued.

Dr. Marie Paule Richard, Chief Medical Officer at TiGenix stated that, "our study is, to our knowledge, the first large-scale, randomized placebo-controlled clinical trial to use clinical assessment of a fistula closure and MRI assessment of absence of abscesses as recommended in the European Crohn's and Colitis Organization guidelines.<sup>6</sup>" Last month, TiGenix entered into a licensing agreement with Takeda, a global leader in gastroenterology, under which Takeda acquired the exclusive right to develop and commercialize Cx601 for complex perianal fistulas in Crohn's disease outside the United States. Based on the data from this pivotal Phase 3 trial in Europe, TiGenix submitted a marketing authorization application to the EMA in the first quarter of 2016, and a decision by the EMA could be expected in 2017. If granted, following Marketing Authorization in the European Economic Area Takeda will become the Marketing Authorization holder and will be responsible for all commercialization and regulatory activities.

A pivotal Phase 3 trial for Cx601 for the treatment of complex perianal fistulas is expected to start in the

United States in 2017. In the U.S., TiGenix intends to apply for fast track designation from the U.S. Food and Drug Administration (FDA), which would facilitate and expedite the development and review process in the U.S.

About Takeda Takeda Pharmaceutical Company Limited (TSE: 4502) is a global, R&D-driven pharmaceutical company committed to bringing better health and a brighter future to patients by translating science into life-changing medicines. Takeda focuses its research efforts on oncology, gastroenterology and central nervous system therapeutic areas. It also has specific development programs in specialty cardiovascular diseases as well as late-stage candidates for vaccines. Takeda conducts R&D both internally and with partners to stay at the leading edge of innovation. New innovative products, especially in oncology, central nervous system and gastroenterology, as well as its presence in emerging markets, fuel the growth of Takeda. More than 30,000 Takeda employees are committed to improving quality of life for patients, working with our partners in health care in more than 70 countries. For more information, visit <http://www.takeda.com/news>.

Takeda's Commitment to Gastroenterology Takeda is a global leader in gastroenterology. With expertise spanning more than 25 years, the company's dedication to innovation continues to evolve and have a lasting impact. ENTYVIO® (vedolizumab) demonstrates Takeda's global capabilities and expansion into the specialty care market in gastroenterology and biologics. Designed and developed specifically to target the gastrointestinal (GI) tract, ENTYVIO was launched in 2014 for the treatment of adults with moderate to severe ulcerative colitis and Crohn's disease. TAKECABA® (vonoprazan fumarate) is Takeda's potassium-competitive acid blocker and was launched in Japan in 2015. Takeda also markets motility agent AMITIZA® (lubiprostone), which originally launched in 2006 for the treatment of chronic idiopathic constipation, and received subsequent approval to treat irritable bowel syndrome with constipation and opioid-induced constipation. Preceding these notable launches, Takeda pioneered gastroenterological breakthroughs in proton pump inhibitors beginning in the 1990's with lansoprazole. Through specialized and strategic in-house development, external partnerships, in-licensing and acquisitions, Takeda currently has a number of promising early stage GI assets in development, and remains committed to delivering innovative, therapeutic options for patients with gastrointestinal and liver diseases.

About TiGenix TiGenix NV (Euronext Brussels: TIG) is an advanced biopharmaceutical company focused on developing and commercialising novel therapeutics from its proprietary platforms of allogeneic, or donor-derived, expanded stem cells. Two products from the adipose-derived stem cell technology platform

are currently in clinical development. Cx601 is in Phase III for the treatment of complex perianal fistulas in Crohn's disease patients. Cx611 has completed a Phase I sepsis challenge trial and a Phase I/II trial in rheumatoid arthritis. Effective July 31, 2015, TiGenix acquired Coretherapix, whose lead cellular product, AlloCSC-01, is currently in a Phase II clinical trial in acute myocardial infarction (AMI). In addition, the second product candidate from the cardiac stem cell-based platform acquired from Coretherapix, AlloCSC-02, is being developed in a chronic indication. On July 4, 2016, we entered into a licensing agreement with Takeda, a large pharmaceutical company active in gastroenterology, under which Takeda acquired the exclusive right to commercialize Cx601 for complex perianal fistulas outside the United States. TiGenix is headquartered in Leuven (Belgium) and has operations in Madrid (Spain). For more information, please visit <http://www.tigenix.com/>.

About Cx601 Cx601 is a suspension of allogeneic expanded adipose-derived stem cells (eASC) locally injected. Cx601 is an investigational agent being developed for the treatment of complex perianal fistulas in Crohn's disease patients that failed conventional therapy including antibiotics, immunosuppressant, or anti-TNF therapy. Crohn's disease is a chronic inflammatory disease of the intestine and patients can suffer from complex perianal fistulas for which there is currently no effective treatment. In 2009, the European Commission granted Cx601 orphan designation for the treatment of anal fistulas, recognizing the debilitating nature of the disease and the lack of treatment options. Based on positive Phase 2 results, TiGenix sought scientific advice from the European Medicines Agency (EMA) on the future development path of Cx601. TiGenix then initiated a randomized, double-blind, placebo-controlled Phase 3 trial in Europe and Israel designed to comply with the requirements laid down by the EMA. 'Madrid Network', an organization within the Autonomous Region of Madrid which helps companies to grow through high-technology innovation, issued a soft loan to help finance this Phase 3 study. The program is funded by The Secretary of State for Research, Development and Innovation (Ministry of Economy and Competitiveness) within the framework of the INNTEGRA plan. The study's primary endpoint was combined remission, defined as clinical assessment at week 24 of closure of all treated external openings draining at baseline despite gentle finger compression, and absence of collections >2cm confirmed by MRI. In the 24 weeks results of the Phase 3 study reported in August 2015, Cx601 achieved statistically significant superiority ( $p < 0.025$ ) on the primary endpoint with 49.5% combined remission at week 24 compared to 34.3% in the placebo arm in the ITT population. These results translate into a relative risk of 1.44, meaning that patients receiving Cx601 had a 44% greater probability of achieving combined remission than placebo patients. Efficacy results were robust and consistent across all statistical populations. Treatment emergent adverse events (non-serious and serious) and discontinuations due to adverse events were comparable between Cx601 and placebo arms. The Phase

3 study trial has completed a follow-up analysis at 52 weeks post-treatment. Based on the positive 24 weeks Phase 3 study results, TiGenix has submitted a Marketing Authorization Application to the EMA in early 2016. TiGenix is preparing to develop Cx601 in the U.S. after having reached an agreement with the FDA through a special protocol assessment procedure (SPA) in 2015. On July 4, 2016 TiGenix entered into a licensing agreement with Takeda, a pharmaceutical company leader in gastroenterology, whereby Takeda acquired an exclusive right to commercialize Cx601 for complex perianal fistulas in Crohn's patients outside of the U.S.

###CONTACTS:

For TiGenix: Claudia D'Augusta Chief Financial Officer [claudia.daugusta@tigenix.com](mailto:claudia.daugusta@tigenix.com)+34 91 804 92 64

For Takeda:Tsuyoshi Tada Media in Japan [tsuyoshi.tada@takeda.com](mailto:tsuyoshi.tada@takeda.com)+81 33 278 2417

Elissa Johnsen Media outside of Japan [elissa.johnsen@takeda.com](mailto:elissa.johnsen@takeda.com)+1 224 554 3185

References1. PanÃ©s P, et al. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. The Lancet [online]. Published online July 28, 2016, available at [http://dx.doi.org/10.1016/S0140-6736\(16\)31203-X](http://dx.doi.org/10.1016/S0140-6736(16)31203-X). 2. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004; 350: 876-85. MRI stands for Magnetic Resonance Imaging. 3. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999; 340: 1398-405.4. World IBD Day. Home. Published online July 28, 2016, available at <http://www.worldibdday.org/index.html>. 5. TiGenix Press Release. TiGenix announces positive 52-week Phase III results of Cx601 in complex perianal fistulas in Crohn's disease patients. Last accessed July 29, 2016, available at <http://bit.ly/2aA7DJr6>. 6. Van Assche G, Dignass A, Reinisch W, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: special situations. J Crohns Colitis 2010; 4: 63-101.

This announcement is distributed by NASDAQ OMX Corporate Solutions on behalf of NASDAQ OMX Corporate Solutions clients. The issuer of this announcement warrants that they are solely responsible for the content, accuracy and originality of the information contained therein. Source: TiGenix via GlobenewswireHUG#2032434

<https://www.bioportfolio.com/news/article/2796384/Takeda-TiGenix-Announce-Publication-in-The-Lancet-of-24-Week-Results-of.html>