Takeda and TiGenix Report New Data Highlighting Maintenance of Long-Term Remission of Complex Perianal Fistulas in Crohn's Disease Patients with Cx601

52-week results of the Phase 3 ADMIRE-CD trial presented at the 12th Congress of the European Crohn's and Colitis Organisation (ECCO)

Osaka, Japan, February 17, 2017, and Leuven, Belgium, February 17, 2017, 9:01 am CET – Takeda Pharmaceutical Company Limited (TSE: 4502) ("Takeda") and TiGenix NV (Euronext Brussels and Nasdaq: TIG) ("TiGenix") today announced new data from the Phase 3 ADMIRE-CD clinical trial, which indicated that investigational compound Cx601, a suspension of allogeneic adipose-derived stem cells (eASC), maintained long-term remission of treatment refractory complex perianal fistulas in patients with Crohn's disease over 52 weeks.[1] Results were presented at the 12th Congress of the European Crohn's and Colitis Organisation (ECCO).

The ADMIRE-CD trial is a randomized, double-blind, controlled, Phase 3 trial, designed to investigate the efficacy and safety of the investigational compound Cx601 for the treatment of complex perianal fistulas in patients with Crohn's disease.[2] Patients were randomized to a single administration of Cx601 cells or placebo (control), both added to standard of care. A significantly greater proportion of patients in the Cx601 group versus in the control group achieved clinical and radiological combined remission* (56.3% and 38.6%; p=0.010), and clinical remission (59.2% and 41.6%; p=0.013) at week 52 in the modified intention-to-treat population (mITT).[1] Of those mITT patients who had shown combined remission at week 24, a greater number in the Cx601 group versus the control group reported no relapse at week 52 (75.0% and 55.9%).[1] The rates and types of treatment related adverse events (non-serious and serious) and discontinuations due to adverse events were indicated to be similar in both groups (Cx601: 20.4%; control: 26.5%).[1]

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract, which is thought to affect up to 1.6 million people in Europe.[3] Complex perianal fistulas are a complication for people living with Crohn's disease and there are limited treatment options. Recognizing the rare and debilitating nature of the disorder and lack of treatment options, in 2009 the European Commission granted Cx601 orphan designation for the treatment of perianal fistula. In March 2016, TiGenix announced that it submitted the Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) for Cx601, and a decision by the EMA is expected in 2017. Additionally, in September 2016 orphan drug status was received from the Swiss Agency for Therapeutic Products (Swissmedic) regarding Cx601 for the rare disease complex perianal fistulas in Crohn's disease.[4]

"Perianal fistulizing Crohn's disease is difficult to treat with currently available therapies and often leads to pain, swelling, infection and incontinence," said Dr. Asit Parikh, head of Takeda's Gastroenterology Therapeutic Area Unit. "Existing therapies are limited and associated with–complications and a high failure rate. Cx601 may offer patients an alternative treatment option."

"These data highlight that the efficacy and safety of a single administration of Cx601 were maintained during one year of follow up," said Dr. Marie Paule Richard, Chief Medical Officer at TiGenix. "It is important to also note that the definition of combined remission used in the ADMIRE-CD study, which

* defined as clinical assessment of closure of all treated external openings draining at baseline, despite gentle finger compression, and absence of collections >2cm confirmed by MRI

includes both clinical and radiological assessment by MRI, is more stringent than the criteria commonly used in previous large scale, randomized clinical trials evaluating perianal fistulas in Crohn's disease, based only on clinical assessment."

A global pivotal Phase 3 trial for US registration with Cx601 for the treatment of complex perianal fistulas is expected to be initiated by TiGenix 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.

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. TAKECAB® (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 Takeda Pharmaceutical Company

Takeda Pharmaceutical Company Limited 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 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.

About TiGenix

TiGenix NV (Euronext Brussels and Nasdaq: TIG) is an advanced biopharmaceutical company focused on developing and commercializing novel therapeutics from its proprietary platforms of allogeneic, or donor-derived, expanded stem cells. Our lead product candidate from the adipose-derived stem cell technology platform is Cx601, which is in registration with the EMA for the treatment of complex perianal fistulas in Crohn's disease patients. Our adipose-derived stem cell product candidate 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 candidate, AlloCSC-01, is currently in a Phase II clinical trial in acute myocardial infarction. 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, TiGenix entered into a licensing agreement with Takeda, a large pharmaceutical company active in gastroenterology, under which Takeda acquired the

exclusive right to develop and commercialize Cx601 for complex perianal fistulas outside the United States. TiGenix is headquartered in Leuven (Belgium) and has operations in Madrid (Spain).

About Cx601

Cx601 is a suspension of allogeneic expanded adipose-derived stem cells (eASC) locally injected. Cx601 is an investigational compound being developed in Crohn's disease for the treatment of complex perianal fistulas showing inadequate response to at least one conventional or biologic therapy including antibiotics, immunosuppressants, or anti-TNF agents. Crohn's disease is a chronic inflammatory disease of the intestine and, as a complication of it, 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. Cx601 has met the primary end-point in the Phase 3 ADMIRE-CD study, a randomized, double-blind, controlled trial run in Europe and Israel and designed to comply with the requirements laid down by the EMA. 'Madrid Network' issued a soft loan to help finance this Phase 3 study, which was funded by the Secretary of State for Research, Development and Innovation (Ministry of Economy and Competitiveness) within the framework of the INNTEGRA plan. In this trial, patients were randomized to a single administration of Cx601 cells or placebo (control), both added to standard of care. 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 ITT population (n=212), Cx601 achieved statistically significant superiority (p=0.024) on the primary endpoint with 50% combined remission at week 24 compared to 34% in the control arm. 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 control arms. The 24-week results have been published by *The Lancet*, one of the most highly regarded and well known medical journals in the world. The Phase 3 study has completed a follow-up analysis at 52 weeks confirming its sustained efficacy and safety profile. Top line follow-up data showed that in the ITT population Cx601 achieved statistical superiority (p=0.012) with 54% combined remission at week 52 compared to 37% in the control arm. Long term results also showed that, of patients with combined remission at week 24, a higher proportion of patients treated with Cx601 had no relapse at week 52 (75.0% vs. 55.9%). Based on the positive 24-weeks Phase III 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 develop and commercialize Cx601 for complex perianal fistulas in Crohn's patients outside of the U.S.

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[2] Clinicaltrials.gov. Adipose Derived Mesenchymal Stem Cells for Induction of Remission in Perianal Fistulizing Crohn's Disease (ADMIRE-CD). https://clinicaltrials.gov/ct2/show/NCT01541579?term=cx601&rank=2. [Accessed February 9, 2017]
[3] Burisch, J, Jess, T, Martinato, M, Lakatos, P, on behalf of ECCO – EpiCom. The burden of inflammatory bowel disease in Europe. *Journal of Crohn's and Colitis* 2013; 7: 322 – 337
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