**Takeda and Portal Instruments Announce Collaboration to Develop Needle-Free Drug Delivery Device**

**Osaka, Japan and Cambridge, MA – November 7, 2017 –** Takeda Pharmaceutical Company Limited (TSE: 4502) and Portal Instruments today announced a collaboration to develop and commercialize Portal's needle-free drug delivery device for potential use with Takeda's investigational or approved biologic medicines. The Portal device was developed at the Massachusetts Institute of Technology (MIT) in the laboratory of Professor Ian Hunter. The technology has the potential for applications across a range of biologic medicines that currently require administration through an injection.

The first Takeda development program to potentially utilize this device will be for investigational use with Entyvio® (vedolizumab), a monoclonal antibody for adults with moderately to severely active ulcerative colitis (UC) or Crohn's disease (CD), which is currently administered through intravenous infusion. A Phase III clinical trial program is currently evaluating the efficacy and safety of a subcutaneous formulation of vedolizumab in adults with moderately to severely active UC or CD.

"There is a need for options to keep improving the experience for patients with life-long, chronic conditions that are managed with the intravenous infusions of biologic medicines," said Stefan Koenig, Global Program & Brand Lead at Takeda. "This partnership with Portal demonstrates Takeda's leadership in supporting patients with GI diseases and our commitment to evolve the management of these diseases, such as inflammatory bowel disease, by potentially offering patients the ability to administer treatment in their own at home with a needle-free system."

"Working with Takeda to adapt the Portal device underscores our mission to empower patients with a leading, next-generation drug delivery platform for self-administration that is designed to reduce the pain and anxiety associated with needle injections in addition to reducing administration time," said Patrick Anquetil, CEO of Portal. "This partnership allows us to work collaboratively with Takeda's highly experienced R&D team and provides the first opportunity to introduce the Portal device to patients, a pivotal step as we continue to expand its potential and grow our business."

Portal's needle-free drug delivery device delivers the biologic through a pressurized liquid instead of a needle, and has been clinically shown to be less painful and preferred by patients compared to a standard needle-based injection.[1] This needle-free device is expected to be self-administered by patients at home.

Under terms of the agreement, Portal will receive an initial payment with the potential to earn additional payments of up to $100 million subject to achievement of specified development, regulatory and sales-based milestones and royalties.

**About Entyvio® (vedolizumab)**

Vedolizumab is a prescription medicine approved for adults with moderate to severe ulcerative colitis (UC) or Crohn's disease (CD).[2,3] In people with UC and CD, there's an increased number of inflammatory white blood cells entering the mucosal lining of the bowel.[4] The presence of these inflammatory cells can

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[1] Kojic, et al. An Innovative Needle-free Injection System: Comparison to 1 ml Standard, 1 May 2017, AAPS *PharmSciTech* (# 2017).

[2] Entyvio® Patient Information Leaflet. Takeda Pharmaceuticals. June 2016.

[3] Entyvio® Summary of Product Characteristics. Takeda Pharmaceuticals. June 2014.

[4] Soler D, Chapman T, Yang LL, et al. The binding specificity and selective antagonism of vedolizumab, an anti-α4β7 integrin therapeutic antibody in development for inflammatory bowel diseases. *J Pharmacol Exp Ther*. 2009; 330: 864-875.

lead to the symptoms most commonly seen in people who have UC or CD.[5,6,7] Vedolizumab is designed to reduce this inflammation by blocking the movement of the white blood cells into the inflamed gut tissue.[4] Mucosal addressin cell adhesion molecule 1 (MAdCAM-1) is preferentially expressed on the endothelial lining of blood vessels in the lymphoid tissue of the bowel.[8] The alpha4beta7 (α4β7) integrin is expressed on a subset of circulating white blood cells.[4] Vedolizumab specifically binds to the α4β7 integrin and blocks its interaction with MAdCAM-1, therefore inhibiting the white blood cells from entering the inflamed gut tissue, thus decreasing inflammation.[4]

**About Ulcerative Colitis and Crohn's Disease**

Ulcerative colitis (UC) and Crohn's disease (CD) are two of the most common forms of inflammatory bowel disease (IBD).[9,10] Both UC and CD are chronic, relapsing, remitting, inflammatory conditions of the gastrointestinal (GI) tract that are often progressive in nature.[4,11] UC only involves the large intestine as opposed to CD which can affect any part of the GI tract from mouth to anus.[7,12] CD can also affect the entire thickness of the bowel wall, while UC only involves the innermost lining of the large intestine.[7] UC often presents with symptoms of abdominal discomfort, loose bowel movements, including blood or pus.[7,13] CD commonly presents with symptoms of abdominal pain, diarrhea and weight loss.[5] The cause of UC or CD is not fully understood, however recent research suggests hereditary, genetics, environmental factors and/or an abnormal immune response to microbial antigens in genetically predisposed individuals can lead to UC or CD.[7,14,15]

**Therapeutic Indications**

***Ulcerative colitis***
Vedolizumab is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNFα) antagonist.

***Crohn's disease***
Vedolizumab is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNFα) antagonist.

**Important Safety Information**

**Contraindications**
Hypersensitivity to the active substance or to any of the excipients.

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[5] Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet*. 2012; 380:1590-1605.

[6] Xavier RJ, Podolski DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature*. 2007; 448: 427-434.

[7] Ordas I, Eckmann L, Talamini M, Baumgart DC, Sandborn, WJ. Ulcerative colitis. *Lancet*. 2012; 380: 1606-19.

[8] Briskin M, Winsor-Hines D, Shyjan A, et al. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. *Am J Pathol*. 1997; 151: 97-110.

[9] What is Inflammatory Bowel Disease (IBD)? Centers for Disease Control and Prevention Web site. https://www.cdc.gov/ibd/. Accessed April 24, 2017.

[10] Baumgart DC, Carding SR. Inflammatory bowel disease: cause and immunobiology. *Lancet*. 2007; 369: 1627-1640.

[11] Torres J, Billioud V, Sachar DB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis as a progressive disease: the forgotten evidence. *Inflamm Bowel Dis*. 2012; 18: 1356-1363.

[12] Feuerstein JD, Cheifetz AS. Crohn's disease: Epidemiology, diagnosis and management. *Mayo Clin Proc*. 2017; 92(7): 1088-1103.

[13] Sands BE. From symptom to diagnosis: clinical distinctions among various forms of intestinal inflammation. *Gastroenterology*. 2004; **126:** 1518-1532.

[14] Henckaerts L, Pierik M, Joossens M, et al. Mutations in pattern recognition receptor genes modulate seroreactivity to microbial antigens in patients with inflammatory bowel disease. *Gut.* 2007; 56: 1536-1542.

[15] Kaser A, Zeissig S, Blumberg RS. Genes and environment: How will our concepts on the pathophysiology of IBD develop in the future? *Dig Dis*. 2010; 28: 395-405.

**Special warnings and special precautions for use**
Vedolizumab should be administered by a healthcare professional equipped to manage hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measures should be available for immediate use when administering vedolizumab. Observe all patients during infusion and until the infusion is complete.

**Infusion-related reactions**
In clinical studies, infusion-related reactions (IRR) and hypersensitivity reactions have been reported, with the majority being mild to moderate in severity. If a severe IRR, anaphylactic reaction, or other severe reaction occurs, administration of vedolizumab must be discontinued immediately and appropriate treatment initiated (e.g., epinephrine and antihistamines). If a mild to moderate IRR occurs, the infusion rate can be slowed or interrupted and appropriate treatment initiated (e.g., epinephrine and antihistamines). Once the mild or moderate IRR subsides, continue the infusion. Physicians should consider pre-treatment (e.g., with antihistamine, hydrocortisone and/or paracetamol) prior to the next infusion for patients with a history of mild to moderate IRR to vedolizumab, in order to minimize their risks.

**Infections**
Vedolizumab is a gut-selective integrin antagonist with no identified systemic immunosuppressive activity. Physicians should be aware of the potential increased risk of opportunistic infections or infections for which the gut is a defensive barrier. Vedolizumab treatment is not to be initiated in patients with active, severe infections such as tuberculosis, sepsis, cytomegalovirus, listeriosis, and opportunistic infections until the infections are controlled, and physicians should consider withholding treatment in patients who develop a severe infection while on chronic treatment with vedolizumab. Caution should be exercised when considering the use of vedolizumab in patients with a controlled chronic severe infection or a history of recurring severe infections. Patients should be monitored closely for infections before, during and after treatment. Before starting treatment with vedolizumab, screening for tuberculosis may be considered according to local practice. Some integrin antagonists and some systemic immunosuppressive agents have been associated with progressive multifocal leukoencephalopathy (PML), which is a rare and often fatal opportunistic infection caused by the John Cunningham (JC) virus. By binding to the α4β7 integrin expressed on gut-homing lymphocytes, vedolizumab exerts an immunosuppressive effect on the gut. Although no systemic immunosuppressive effect was noted in healthy subjects, the effects on systemic immune system function in patients with inflammatory bowel disease are not known. No cases of PML were reported in clinical studies of vedolizumab however, healthcare professionals should monitor patients on vedolizumab for any new onset or worsening of neurological signs and symptoms, and consider neurological referral if they occur. If PML is suspected, treatment with vedolizumab must be withheld; if confirmed, treatment must be permanently discontinued. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body, clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months.

**Malignancies**
The risk of malignancy is increased in patients with ulcerative colitis and Crohn's disease. Immunomodulatory medicinal products may increase the risk of malignancy.

**Prior and concurrent use of biological products**
No vedolizumab clinical trial data are available for patients previously treated with natalizumab. Caution should be exercised when considering the use of vedolizumab in these patients. No clinical trial data for concomitant use of vedolizumab with biologic immunosuppressants are available. Therefore, the use of vedolizumab in such patients is not recommended.

**Vaccinations**
Prior to initiating treatment with vedolizumab all patients should be brought up to date with all recommended immunizations. Patients receiving vedolizumab may receive non-live vaccines (e.g., subunit or inactivated vaccines) and may receive live vaccines only if the benefits outweigh the risks.

**Adverse Reactions include:** Nasopharyngitis, Headache, Arthralgia, Upper respiratory tract infection, Bronchitis, Influenza, Sinusitis, Cough, Oropharyngeal pain, Nausea, Rash, Pruritus, Back pain, Pain in extremities, Pyrexia, and Fatigue.

**Please consult with your local regulatory agency for approved labeling in your country**.

**For U.S. audiences, please see the full Prescribing Information including Medication Guide for ENTYVIO®.**

**For EU audiences, please see the Summary of Product Characteristics (SmPC) for ENTYVIO®.**

**Takeda's Commitment to Gastroenterology**
More than 70 million people worldwide are impacted by gastrointestinal (GI) diseases, which can be complex, debilitating and life-changing.[16] Takeda is driven to improving the lives of patients with GI diseases through innovative medicines, dedicated patient disease management support and the evolution of the healthcare environment. Takeda is leading in gastroenterology through the delivery of innovative medicines in areas associated with high unmet needs, such as inflammatory bowel disease, acid-related diseases and motility disorders. Our GI research & development team is also exploring solutions in celiac disease and liver diseases, as well as scientific advancements through microbiome therapies. With more than 25 years of experience in this area, our broad approach to treating many diseases that impact the GI system and our global network of collaborators, Takeda aims to advance how patients manage their disease.

**About Takeda Pharmaceutical Company**
Takeda Pharmaceutical Company Limited is a global, research and development-driven pharmaceutical company committed to bringing better health and a brighter future to patients by translating science into life-changing medicines. Takeda focuses its R&D efforts on oncology, gastroenterology and central nervous system therapeutic areas plus 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 Takeda's presence in Emerging Markets, are currently fueling the growth of Takeda. More than 30,000 Takeda employees are committed to improving quality of life for patients, working with Takeda's partners in health care in more than 70 countries. For more information, visit www.takeda.com/news.

**Takeda's Forward-Looking Statements**
This press release contains "forward-looking statements." Forward-looking statements include all statements other than statements of historical fact, including plans, strategies and expectations for the future, statements regarding the expected timing of filings and approvals relating to the transaction, the expected timing of the completion of the transaction, the ability to complete the transaction or to satisfy the various closing conditions, future revenues and profitability from or growth or any assumptions underlying any of the foregoing. Statements made in the future tense, and words such as "anticipate," "expect," "project," "continue," "believe," "plan," "estimate," "pro forma," "intend," "potential," "target," "forecast," "guidance," "outlook," "seek," "assume," "will," "may," "should," and similar expressions are intended to qualify as forward-looking statements. Forward-looking statements are based on estimates and assumptions made by management that are believed to be reasonable, though they are inherently uncertain and difficult to predict. Investors and security holders are cautioned not to place undue reliance on these forward-looking statements.

Forward-looking statements involve risks and uncertainties that could cause actual results or experience to differ materially from that expressed or implied by the forward-looking statements. Some of these risks and uncertainties include, but are not limited to: required regulatory approvals for the transaction may not be obtained in a timely manner, if at all; the conditions to closing of the transaction may not be satisfied;

[16] Digestive Health. University of Miami Hospital. http://umiamihospital.com/service-lines/digestive-health. Accessed April 24, 2017.

competitive pressures and developments; applicable laws and regulations; the success or failure of product development programs; actions of regulatory authorities and the timing thereof; changes in exchange rates; and claims or concerns regarding the safety or efficacy of marketed products or product candidates in development. The forward-looking statements contained in this press release speak only as of the date of this press release, and neither Portal Instruments nor Takeda undertake any obligation to revise or update any forward-looking statements to reflect new information, future events or circumstances after the date of the forward-looking statement. If one or more of these statements is updated or corrected, investors and others should not conclude that additional updates or corrections will be made.

**About Portal Instruments**
Portal Instruments is a Series B funded medical device company focused on advanced drug delivery and backed by strategic and venture investors. Portal Instruments is developing and commercializing a highly innovative needle-free drug delivery platform technology to transform the administration of medicines and improve the patient experience for chronic diseases. Real time tracking and reporting sets a new standard for interactivity between the patient and care teams, monitoring adherence and potentially improving patient outcomes. Portal Instruments' Quality Management System is ISO 13485 certified. For more information, please visit www.portalinstruments.com or follow @portalcambridge on Twitter.

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