FDA Advisory Committee Recommends Approval of Takeda's Investigational Biologic Vedolizumab

Takeda announces positive vote on vedolizumab to treat ulcerative colitis and Crohn's disease

Deerfield, Ill., December 9, 2013 and Osaka, Japan, December 10, 2013 -- Takeda Pharmaceutical Company Limited ("Takeda") and its wholly-owned subsidiary, Takeda Pharmaceuticals U.S.A., Inc., today announced that a joint panel of members from the Gastrointestinal Drugs and Drug Safety and Risk Management Advisory Committees of the United States (U.S.) Food and Drug Administration (FDA) voted to recommend approval of Takeda's vedolizumab for the treatment of adults with moderately to severely active ulcerative colitis (UC) and Crohn's disease (CD). All 21 committee members voted that based on currently available efficacy and safety data, the benefits outweigh the potential risks of vedolizumab to support approval for UC. Specifically, 13 committee members supported approval for UC patients who have failed steroids or immunosuppressants or TNF-α antagonists, while eight committee members supported approval for UC patients who have failed immunosuppressants or TNF-α antagonists (the indicated population would not include patients that failed steroids only). Twenty of the 21 committee members voted to support approval for CD. Specifically, 14 committee members supported approval for CD patients who have failed steroids or immunosuppressants or TNF-α antagonists while six supported approval for CD patients who have failed immunosuppressants or TNF-α antagonists (the indicated population would not include patients that failed steroids only).

"We are very pleased with the advisory committee's recommendation. People with ulcerative colitis or Crohn's disease are in need of additional treatment options, as many patients lose response to currently available treatments," said Asit Parikh, M.D., Ph.D., vice president, general medicine, Takeda. "Vedolizumab was designed to treat inflammation in the GI tract, and if approved, may offer an additional option for patients suffering from ulcerative colitis or Crohn's disease."

Without asking for a vote, the FDA also requested feedback from panel members about what post-market risk mitigation strategies beyond labeling, if any, would be needed to ensure that the benefits of vedolizumab outweigh its risks. Takeda will continue to work closely with the FDA on an appropriate Risk Evaluation Mitigation Strategy (REMS) for vedolizumab.

The outcome of the advisory committee meeting, which included five voting questions, is non-binding and will be taken into consideration by the FDA when making its decision on Takeda's Biologics License Application (BLA) for vedolizumab, which was submitted in June 2013. The FDA granted vedolizumab Priority Review status for the proposed indication in UC in September 2013 and standard review for the indication of CD. Priority Review status is given to applications for investigational drugs that treat a serious condition and, if approved, would provide a significant improvement in safety or effectiveness.[1]

The BLA filings were supported by the GEMINI™ Studies, a four-study clinical program investigating vedolizumab in 2,700 patients in nearly 40 countries, making it the largest Phase 3 clinical trial program conducted to date simultaneously evaluating both UC and CD patient populations.[2,3,4] Enrolled patients had failed at least one conventional therapy, including glucocorticoids, immunomodulators and/or a tumor necrosis factor-alpha (TNF-α) antagonist. TNF-α antagonist and conventional therapy failure patients included those with inadequate response (primary non-responders), loss of response (secondary non-responders) or those who were intolerant.[5,6,7]

About ulcerative colitis and Crohn's disease

Ulcerative colitis (UC) and Crohn's disease (CD) are the two most common forms of inflammatory bowel disease (IBD), which is marked by inflammation in the GI tract.[8] UC impacts the large intestine only, which includes the colon and the rectum.[9] The most common symptoms of UC include abdominal discomfort and blood or pus in diarrhea.[10] CD can impact any part of the digestive tract and common symptoms may include abdominal pain, diarrhea, rectal bleeding, weight loss, and fever.[11] There is no known cause for UC or CD, although many researchers believe that the interaction between genes, the body's immune system, and environmental factors may play a role.[12] The aim of UC and CD treatments is to induce and maintain remission, or achieve extended periods of time when patients do not experience symptoms.[13,14]

About vedolizumab

Vedolizumab, under development for the treatment of UC and CD, is a humanized monoclonal antibody that specifically antagonizes the alpha4beta7 (α4β7) integrin, inhibiting the binding of α4β7 to intestinal mucosal addressin cell adhesion molecule 1 (MAdCAM-1).[15] MAdCAM-1 is preferentially expressed on blood vessels and lymph nodes of the gastrointestinal tract.[16] The α4β7 integrin is expressed on a subset of circulating white blood cells.[17] These cells have been

shown to play a role in mediating the inflammatory process in UC and CD.[18,19] By inhibiting α4β7, vedolizumab may limit the ability of certain lymphocytes to infiltrate gut tissues.[20]

About Takeda Pharmaceuticals U.S.A., Inc.

Takeda is a research-based global company with its main focus on pharmaceuticals. As the largest pharmaceutical company in Japan and one of the global leaders of the industry, Takeda is committed to strive towards better health for people worldwide through leading innovation in medicine.

The company has a commercial presence covering around 70 countries, with particular strength in Asia, North America, Europe and fast-growing emerging markets including Latin America, Russia-CIS and China. Takeda is ranked 15th globally. Areas of focus include cardiovascular and metabolic, oncology, respiratory and immunology, central nervous system, general medicine, and vaccines.

Through the integration of Millennium Pharmaceuticals and Nycomed, Takeda has been transforming itself, broadening its therapeutic expertise and geographic outreach.

Takeda Pharmaceuticals U.S.A., Inc. is located in Deerfield, Ill., and is the U.S. marketing and sales organization of Takeda Pharmaceutical Company Limited.

Additional information about Takeda is available through its corporate website, **www.takeda.com**, and additional information about Takeda Pharmaceuticals U.S.A., Inc. is available through its website, www.takeda.us.

About Takeda Pharmaceutical Company Limited

Located in Osaka, Japan, Takeda is a research-based global company with its main focus on pharmaceuticals. As the largest pharmaceutical company in Japan and one of the global leaders of the industry, Takeda is committed to strive towards better health for people worldwide through leading innovation in medicine. Additional information about Takeda is available through its corporate website, www.takeda.com.

This press release contains forward-looking statements. Forward-looking statements include statements regarding Takeda's plans, outlook, strategies, results for the future, and other statements that are not descriptions of historical facts. Forward-looking statements may be

identified by the use of forward-looking words such as "may," "believe," "will," "expect," "project," "estimate," "should," "anticipate," "plan," "assume," "continue," "seek," "pro forma," "potential," "target," "forecast," "guidance," "outlook" or "intend" or other similar words or expressions of the negative thereof. 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 are cautioned not to unduly rely on such 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, (1) the economic circumstances surrounding Takeda's business, including general economic conditions in Japan, the United States and worldwide; (2) competitive pressures and developments; (3) applicable laws and regulations; (4) the success or failure of product development programs; (5) actions of regulatory authorities and the timing thereof; (6) changes in exchange rates; (7) claims or concerns regarding the safety or efficacy of marketed products or product candidates in development; and (8) integration activities with acquired companies.

The forward-looking statements contained in this press release speak only as of the date of this press release, and Takeda undertakes no 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 Takeda does update or correct one or more of these statements, investors and others should not conclude that Takeda will make additional updates or corrections.

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[1] United States Food and Drug Administration. Office of New Drugs Review Designation Policy: Priority (P) and Standard (S). http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm082000.pdf. Updated June 25, 2013. Accessed August 22, 3013.
[2] Data on File: Vedolizumab Integrated Summary of Safety.
[3] REMICADE Prescribing Information. Horsham, PA: Janssen Biotech, Inc.; March 2013.
[4] HUMIRA Prescribing Information. North Chicago, IL: AbbVie Inc.; April 2013.
[5] Data on File: Final Clinical Study Report C13006. 2012.
[6] Data on File: Final Clinical Study Report C13007. 2012.
[7] Data on File: Final Clinical Study Report C13011. 2012.
[8] Knigge KL. Inflammatory bowel disease. *Clin Cornerstone*. 2002;4(4):49-60.
[9] National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, National Digestive Diseases Information Clearinghouse. Ulcerative colitis. http://digestive.niddk.nih.gov/ddiseases/pubs/colitis/index.aspx. Published October 2011. Accessed March 1, 2013
[10] National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, National Digestive Diseases Information Clearinghouse. Ulcerative colitis. http://digestive.niddk.nih.gov/ddiseases/pubs/colitis/index.aspx. Published October 2011. Accessed March 1, 2013
[11] National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, National Digestive Diseases Information Clearinghouse. Crohn's disease. http://digestive.niddk.nih.gov/ddiseases/pubs/crohns/index.aspx. Published December 2011. Accessed March 1, 2013.
[12] Crohn's and Colitis Foundation of America. The facts about inflammatory bowel diseases. http://www.ccfa.org/assets/pdfs/ibdfactbook.pdf. Published June, 2011. Accessed January 4, 2013.
[13] National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, National Digestive Diseases Information Clearinghouse. Crohn's disease. http://digestive.niddk.nih.gov/ddiseases/pubs/crohns/index.aspx. Published December 2011. Accessed March 1, 2013.
[14] National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, National Digestive Diseases Information Clearinghouse. Ulcerative colitis. http://digestive.niddk.nih.gov/ddiseases/pubs/colitis/index.aspx. Published October 2011. Accessed March 1, 2013
[15] Soler D, Chapman T, Yang L, 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(3):864-875. http://jpet.aspetjournals.org/content/330/3/864.full.pdf+html. Published June 9, 2009. Accessed March 1, 2013.
[16] Briskin M, Winsor-Hines D, Syjan A, et al. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. American Journal of Pathology. 1997;51(1):97.
[17] Soler D, Chapman T, Yang L, 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(3):864-875. http://jpet.aspetjournals.org/content/330/3/864.full.pdf+html. Published June 9, 2009. Accessed March 1, 2013.
[18] Soler D, Chapman T, Yang L, 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(3):864-875. http://jpet.aspetjournals.org/content/330/3/864.full.pdf+html. Published June 9, 2009. Accessed March 1, 2013.
[19] Gledhill T, Bodger K. New and emerging treatments for ulcerative colitis: a focus on vedolizumab. *Biologics: targets and therapy*. 2013;7:123-130.
[20] Soler D, Chapman T, Yang L, 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(3):864-875. http://jpet.aspetjournals.org/content/330/3/864.full.pdf+html. Published June 9, 2009. Accessed March 1, 2013.