Better Health, Brighter Future

Takeda Announces Positive Results in Phase 2b Study of Investigational TAK-279, an Oral, Once-Daily TYK2 Inhibitor, in People with Moderate-to-Severe Plaque Psoriasis

OSAKA, Japan, March 20, 2023, and CAMBRIDGE, Massachusetts, March 19, 2023 – Takeda (TSE:4502/NYSE:TAK) today announced positive results from a Phase 2b clinical trial of TAK-279 (NDI-034858), a highly selective, oral allosteric tyrosine kinase 2 (TYK2) inhibitor, in patients with moderate-to-severe plaque psoriasis. The results was presented on March 18, 2023 (ET). Please see the attached press release for details.

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News Release

Takeda Announces Positive Results in Phase 2b Study of Investigational TAK-279, an Oral, Once-Daily TYK2 Inhibitor, in People with Moderate-to-Severe Plaque Psoriasis

- *Results for TAK-279 (Formerly NDI-034858) Show a Significantly Greater Proportion of Patients Achieved Psoriasis Area and Severity Index (PASI) 75 at Doses ≥5mg at 12 Weeks*[1]
- *At the Highest Dose of TAK-279, 46% of Patients Achieved PASI 90 and 33% Achieved PASI 100 at 12 Weeks, Indicating a Near-Total or Total Clearance of Skin Lesions*[1]
- *Takeda to Start Phase 3 Plaque Psoriasis Study and Expects Topline Results for a Phase 2b Study in Psoriatic Arthritis in FY2023*
- *Takeda Will Evaluate TAK-279 in Additional Immune-Mediated Diseases Including Systemic Lupus Erythematosus (SLE) and Inflammatory Bowel Disease (IBD), and Explore Further Indications in the Future*

OSAKA, Japan, March 20, 2023, and CAMBRIDGE, Massachusetts, March 19, 2023 – Takeda (TSE:4502/NYSE:TAK) today announced positive results from a Phase 2b clinical trial of TAK-279 (NDI-034858), a highly selective, oral allosteric tyrosine kinase 2 (TYK2) inhibitor, in patients with moderate-to-severe plaque psoriasis. The study met its primary and secondary endpoints, with a statistically significant greater proportion of TAK-279 patients achieving Psoriasis Area and Severity Index (PASI) 75, 90 and 100 in the 5mg, 15mg and 30mg dosing arms compared to placebo at 12 weeks.[1] These data were presented during a late-breaking session at the American Academy of Dermatology (AAD) Annual Meeting being held March 17-21, 2023 in New Orleans.

"The Phase 2b TAK-279 results demonstrate a strong overall clinical benefit and, importantly, a significant number of patients reached PASI 90 or 100, achieving near-total or total skin clearance," said April Armstrong, M.D., MPH, clinical investigator in the Phase 2b study and Associate Dean and Professor of Dermatology at the University of Southern California. "These results further support the potential of highly selective TYK2 inhibition to provide an effective and convenient oral treatment option for people living with moderate-to-severe plaque psoriasis who are not achieving optimal skin clearance with current therapies. I look forward to the results of future clinical trials."

In the Phase 2b study, 259 patients were randomized (1:1:1:1:1 ratio) to receive one of four doses of TAK-279 once-daily, or placebo for 12 weeks.[1] Results showed:

- A significantly greater proportion of TAK-279 patients achieved PASI 75 (44%, 68%, 67%; 5mg, 15mg, 30mg, respectively) versus placebo (6%; $p<0.001$), meeting the study's primary endpoint.[1]
- A significantly greater proportion of TAK-279 patients achieved PASI 90 (21%, 45%, 46%; 5mg, 15mg, 30mg, respectively) versus placebo (0%; $p<0.001$), and PASI 100 (10%, 15%, 33%; 5mg, 15mg, 30mg, respectively) versus placebo (0%; $p<0.001$ at 30mg).[1]
- A significantly greater proportion of TAK-279 patients achieved Physician Global Assessment (PGA) scores of 0/1 (27%, 49%, 52%; 5mg, 15mg, 30mg, respectively) or 0 (10%, 15%, 33%; 5mg, 15mg, 30mg, respectively) versus placebo (4% [$p\leq0.001$] and 0% [$p<0.001$ at 30mg],

respectively) at 12 weeks.[1] A PGA score of 1 indicates almost clear skin and 0 indicates totally clear skin.[2]
- There were no statistically significant differences in PASI or PGA response rates seen in the TAK-279 2mg arm* (18%, 2%, 10%, 2%; PASI 75, PASI 100, PGA 0/1, PGA 0, respectively) compared to placebo.[1]

The frequency of adverse events (AEs) was 53-62% in the treatment arms and 44% in the placebo arm. Most events were mild to moderate in severity. Two serious AEs occurred in one patient (15mg) and were considered unrelated. Changes in laboratory parameters were consistent with known effects of allosteric TYK2 inhibition.[1]

"These compelling TAK-279 data strengthen its potential for people with moderate-to-severe plaque psoriasis. The highly selective TYK2 inhibition seen with TAK-279 spares inhibition of other members of the Janus kinase (JAK) family, which we believe should avoid JAK-related toxicities," said Andy Plump, President R&D, Takeda. "We are confident that we can execute a comprehensive development program and deliver a potential best-in-class therapy for patients, given Takeda's strong background in immune-mediated diseases, including inflammatory bowel disease."

Based on these Phase 2b results, Takeda will initiate a Phase 3 study of TAK-279 in psoriasis in FY2023. Takeda expects topline results from a Phase 2b study in psoriatic arthritis in FY2023 and will be evaluating TAK-279 in additional immune-mediated diseases including systemic lupus erythematosus (SLE) and inflammatory bowel disease (IBD). Other indications will be explored in the future.

Results from the Phase 2b study have no impact on the full year consolidated reported forecast for the fiscal year ending March 31, 2023 (Fiscal Year 2022).

*In the TAK-279 2mg arm, the PASI 90 response rate was 8% with a nominal p-value = 0.037 compared to placebo.[1]

About Plaque Psoriasis
Psoriasis is a chronic autoimmune disease in which the body's immune system causes skin cells to multiply too quickly.[3] Plaque psoriasis is a common form of psoriasis and is characterized by raised, red patches of skin that are covered by silvery-white scales which can be itchy and painful.[3,4] Plaque psoriasis most often appears on the scalp, elbows, knees and lower back, but can appear anywhere on the body.[3-5] Globally, an estimated 125 million people are living with psoriasis and about 80-90% of those have plaque psoriasis.[5,6]

About TAK-279
TAK-279 is a late-stage, highly selective, oral allosteric tyrosine kinase 2 (TYK2) inhibitor being evaluated for the treatment of multiple autoimmune diseases.[1,7] In preclinical studies, TAK-279 has demonstrated excellent functional selectivity and wide therapeutic margins.[8] In Phase 1 studies, TAK-279 showed a good tolerability profile, a dose-dependent trend in exploratory clinical activity and a pharmacokinetic profile allowing for once-daily solid oral dosing.[9] TAK-279 is in an ongoing Phase 2b trial in active psoriatic arthritis (NCT05153148). TAK-279 is an investigational compound that has not been approved for use by any regulatory authority.

About the TAK-279 Phase 2b Study in Psoriasis
The Phase 2b study (NCT04999839) was a randomized, multicenter, double-blind, placebo-controlled multiple-dosed trial designed to evaluate the efficacy, safety and tolerability of TAK-279 in subjects with moderate-to-severe plaque psoriasis. 259 patients were randomly assigned (1:1:1:1:1 ratio) to receive one of four doses of TAK-279 (2mg, 5mg, 15mg, 30mg, all once-daily) or placebo for 12 weeks. The primary

endpoint was the proportion of patients achieving Psoriasis Area and Severity Index (PASI) 75 at Week 12.[1]

About Tyrosine Kinase 2 (TYK2) Inhibitors
Tyrosine kinase 2 (TYK2) is an intracellular enzyme that belongs to the Janus family of protein tyrosine kinases.[10] TYK2 is a key part of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway, which mediates several key immune cytokine receptors associated with inflammation.[11] Increased activation of these inflammatory proteins is associated with several autoimmune diseases, including psoriasis, psoriatic arthritis, systemic lupus erythematosus and inflammatory bowel disease.[12] Selective allosteric inhibition of TYK2 may be a promising therapeutic approach to target autoimmune inflammation while potentially avoiding the toxicity associated with JAK inhibitors.[13]

About Takeda
Takeda is a global, values-based, R&D-driven biopharmaceutical leader headquartered in Japan, committed to discover and deliver life-transforming treatments, guided by our commitment to patients, our people and the planet. Takeda focuses its R&D efforts on four therapeutic areas: Oncology, Rare Genetics and Hematology, Neuroscience, and Gastroenterology (GI), with expertise in immune and inflammatory diseases. We also make targeted R&D investments in Plasma-Derived Therapies and Vaccines. We are focusing on developing highly innovative medicines that contribute to making a difference in people's lives by advancing the frontier of new treatment options and leveraging our enhanced collaborative R&D engine and capabilities to create a robust, modality-diverse pipeline. Our employees are committed to improving quality of life for patients and to working with our partners in health care in approximately 80 countries and regions. For more information, visit https://www.takeda.com.

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