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News Release

Protagonist and Takeda Announce Positive Topline Results from Phase 3 VERIFY Study of Rusfertide in Patients with Polycythemia Vera

OSAKA, Japan, March 3, 2025 – Takeda Pharmaceutical Company Limited (TSE:4502/NYSE:TAK) ("Takeda") and Protagonist Therapeutics, Inc. (NASDAQ:PTGX) today announced positive topline results for the Phase 3 VERIFY study of rusfertide in patients with polycythemia vera (PV). Please see the attached press release for details.

The impact on Takeda's financial results for the fiscal year ending March 31, 2025 (FY2024), following the study results, is immaterial.

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- ***Study met the primary endpoint, with a significantly higher proportion of clinical responders on rusfertide compared to placebo***
- ***All four key secondary endpoints were met, including EU primary endpoint and patient-reported outcomes***
- ***Rusfertide was generally well tolerated; no new safety findings were observed in the study***

NEWARK, California, OSAKA, Japan and CAMBRIDGE, Massachusetts, March 3, 2025 – Protagonist Therapeutics, Inc. ("Protagonist") (NASDAQ:PTGX) and Takeda (TSE:4502/NYSE:TAK) today announced positive topline results for the Phase 3 VERIFY study, in which phlebotomy-dependent patients with polycythemia vera (PV) were randomized to treatment with either rusfertide or placebo, as an add-on to standard of care treatment. The study met its primary endpoint and all four key secondary endpoints. Rusfertide is a first-in-class investigational hepcidin mimetic peptide therapeutic, which has received Orphan Drug designation and Fast Track designation from the U.S. Food & Drug Administration (FDA).

Key findings from the study include:

- The primary endpoint of the study was met, with a significantly higher proportion of clinical responders[1] among rusfertide-treated patients with PV (77%) compared to those who received placebo (33%) during weeks 20-32; $p<0.0001$. The primary endpoint of the study was the proportion of patients achieving a response, which was defined as the absence of phlebotomy eligibility.
- The first key secondary endpoint, which is the pre-specified primary endpoint for European Union (EU) regulators, was also met, with a mean of 0.5 phlebotomies per patient in the rusfertide arm compared to 1.8 phlebotomies per patient in the placebo arm during weeks 0-32; $p<0.0001$.
- The other three pre-specified key secondary endpoints, namely hematocrit control[2] and patient-reported outcomes using PROMIS Fatigue SF-8a[3] and MFSAF TSS-7[4], were also achieved with statistical significance.
- Rusfertide was generally well tolerated in the Phase 3 VERIFY trial, and safety was in line with previous rusfertide clinical studies. No new safety findings were observed in the study. The majority of adverse events were grade 1-2 injection site reactions and all serious adverse events

[1] A responder is a patient who completed weeks 0-32 of the study, was not phlebotomy eligible and did not receive a phlebotomy during weeks 20-32. To meet phlebotomy eligibility, patients in the study were required to have: confirmed hematocrit ≥45% that was ≥3% higher than their baseline hematocrit value, or hematocrit ≥48%. See "About VERIFY" below.
[2] Proportion of patients with hematocrit less than 45%.
[3] Mean change from baseline to week 32 using PROMIS Fatigue SF-8a, a questionnaire that measures patient-reported fatigue symptoms and their impact on daily life.
[4] Mean change from baseline to week 32 using MFSAF TSS-7 v. 4.0, a questionnaire that measures patient reporting of seven key symptoms related to myelofibrosis (many of which are common among PV patients as well).

reported were deemed to be not drug related. There was no evidence of an increased risk of cancer in rusfertide-treated patients compared to those on placebo.

"The positive results of the Phase 3 VERIFY study across the primary and all key secondary endpoints provide compelling evidence of the potential for rusfertide as a first-in-class erythrocytosis-specific agent to address unmet medical needs in patients with PV who are unable to achieve adequate hematocrit control despite standard of care treatments," said Arturo Molina, M.D., M.S., Chief Medical Officer of Protagonist. "We plan to submit additional details of these promising results for presentation at upcoming medical conferences in 2025. We are immensely grateful to the patients, study staff and principal investigators who made the VERIFY study possible."

Patients with PV are at increased risk for life-threatening cardiovascular and thrombotic events. Many patients with PV require regular phlebotomy, a process of removing blood to manage elevated hematocrit levels caused by an excess of red blood cells, as well as treatment with cytoreductive therapies. Phlebotomy can be burdensome and exacerbate symptoms, including severe fatigue, visual disturbances and iron deficiency, which impact patients' quality of life. The reduction of hematocrit below 45% is a primary treatment goal for patients with PV as recommended by current treatment guidelines.

"We are encouraged by these results and excited about the potential of rusfertide to help patients living with PV. These patients may experience a high treatment burden, and severe symptoms can impact their quality of life," said Andy Plump, M.D., Ph.D., President of R&D at Takeda. "We are deeply committed to bringing additional treatment options to those living with blood cancers, including myeloid cancers such as PV."

"The totality of impressive clinical data to date shows that rusfertide has the potential for meaningful positive impact on the lives of patients with PV," said Dinesh V. Patel, Ph.D., President and Chief Executive Officer at Protagonist. "We look forward to working with our partner, Takeda, to submit our findings to the regulatory agencies. Today's study results also mark a critical inflection point in Protagonist's decade long journey in the hepcidin program and further validates our platform and expertise in innovating highly differentiated peptide-based medicines to fulfill unmet medical needs."

Under the license and collaboration agreement between Protagonist and Takeda, Protagonist earns a $25 million milestone payment following these positive results. The milestone is payable following completion of the VERIFY clinical study report.

The impact on Takeda's financial results for the fiscal year ending March 31, 2025 (FY2024), following the study results, is immaterial.

Protagonist will host a conference call and webcast, for which details can be found below.

Protagonist Investor Conference Call and Webcast Details

The dial-in numbers for Protagonist's investor update on Monday, March 3rd at 8:30 am ET are:

US-based Investors: 1-877-300-8521
International Investors: 1-412-317-6026
Conference Call ID: 1793905

The webcast link for the event can be found here:
https://viavid.webcasts.com/starthere.jsp?ei=1708360&tp_key=94f2832555

A replay of the presentation will be available on the Protagonist Investor Relations Events and Presentations webpage following the event.

About VERIFY
The Phase 3 VERIFY trial (NCT05210790) is an ongoing, three-part, global, randomized, placebo-controlled trial evaluating rusfertide in 293 patients with polycythemia vera over a 156-week period. The trial is evaluating the efficacy and safety of once-weekly, subcutaneously self-administered rusfertide in patients with uncontrolled hematocrit who are phlebotomy dependent despite standard of care treatment, which could include hydroxyurea, interferon and/or ruxolitinib. The primary endpoint of the study was the proportion of patients achieving a response during weeks 20-32, which was defined as the absence of "phlebotomy eligibility." To meet phlebotomy eligibility, patients in the study were required to have: confirmed hematocrit ≥45% that was ≥3% higher than their baseline hematocrit value, or hematocrit ≥48%.

All patients have completed their participation in the randomized, placebo-controlled portion of the trial evaluating the efficacy and safety of rusfertide plus current treatment versus placebo plus current treatment and are now in the open-label portions of the trial.

About Protagonist
Protagonist Therapeutics is a discovery through late-stage development biopharmaceutical company. Two novel peptides derived from Protagonist's proprietary discovery platform are currently in advanced Phase 3 clinical development, with New Drug Application submissions to the FDA expected in 2025. Icotrokinra (formerly, JNJ-2113) is a first-in-class investigational targeted oral peptide that selectively blocks the Interleukin-23 receptor ("IL-23R") which is licensed to JNJ Innovative Medicines ("JNJ"), formerly Janssen Biotech, Inc. Following icotrokinra's joint discovery by Protagonist and JNJ scientists pursuant to the companies' IL-23R collaboration, Protagonist was primarily responsible for development of icotrokinra through Phase 1, with JNJ assuming responsibility for development in Phase 2 and beyond. Rusfertide, a mimetic of the natural hormone hepcidin, is currently in Phase 3 development for the rare blood disorder polycythemia vera (PV). Rusfertide is being co-developed and will be co-commercialized with Takeda Pharmaceuticals pursuant to a worldwide collaboration and license agreement entered into in 2024 under which the Company remains primarily responsible for development through NDA filing. The Company also has a number of pre-clinical stage oral drug discovery programs addressing clinically and commercially validated targets, including IL-17 oral peptide antagonist PN-881, oral hepcidin program, and oral obesity program.

More information on Protagonist, its pipeline drug candidates and clinical studies can be found on the Company's website at www.protagonist-inc.com.

About Takeda
Takeda is focused on creating better health for people and a brighter future for the world. We aim to discover and deliver life-transforming treatments in our core therapeutic and business areas, including

gastrointestinal and inflammation, rare diseases, plasma-derived therapies, oncology, neuroscience and vaccines. Together with our partners, we aim to improve the patient experience and advance a new frontier of treatment options through our dynamic and diverse pipeline. As a leading values-based, R&D-driven biopharmaceutical company headquartered in Japan, we are guided by our commitment to patients, our people and the planet. Our employees in approximately 80 countries and regions are driven by our purpose and are grounded in the values that have defined us for more than two centuries. For more information, visit www.takeda.com.

Protagonist Cautionary Note on Forward-Looking Statements

This press release contains forward-looking statements for purposes of the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Forward-looking statements include statements regarding the potential benefits of rusfertide and the timing of rusfertide clinical trial data and regulatory submission. In some cases, you can identify these statements by forward-looking words such as "anticipate," "believe," "may," "will," "expect," or the negative or plural of these words or similar expressions. Forward-looking statements are not guarantees of future performance and are subject to risks and uncertainties that could cause actual results and events to differ materially from those anticipated, including, but not limited to, our ability to develop and commercialize our product candidates, our ability to earn milestone payments under our collaboration agreements with Janssen and Takeda, our ability to use and expand our programs to build a pipeline of product candidates, our ability to obtain and maintain regulatory approval of our product candidates, our ability to operate in a competitive industry and compete successfully against competitors that have greater resources than we do, and our ability to obtain and adequately protect intellectual property rights for our product candidates. Additional information concerning these and other risk factors affecting our business can be found in our periodic filings with the Securities and Exchange Commission, including under the heading "Risk Factors" contained in our most recently filed periodic reports on Form 10-K and Form 10-Q filed with the Securities and Exchange Commission. Forward-looking statements are not guarantees of future performance, and our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate, may differ materially from the forward-looking statements contained in this press release. Any forward-looking statements that we make in this press release speak only as of the date of this press release. We assume no obligation to update our forward-looking statements, whether as a result of new information, future events or otherwise, after the date of this press release.

Takeda Important Notice

For the purposes of this notice, “press release” means this document, any oral presentation, any question and answer session and any written or oral material discussed or distributed by Takeda Pharmaceutical Company Limited (“Takeda”) regarding this release. This press release (including any oral briefing and any question-and-answer in connection with it) is not intended to, and does not constitute, represent or form part of any offer, invitation or solicitation of any offer to purchase, otherwise acquire, subscribe for, exchange, sell or otherwise dispose of, any securities or the solicitation of any vote or approval in any jurisdiction. No shares or other securities are being offered to the public by means of this press release. No offering of securities shall be made in the United States except pursuant to registration under the U.S. Securities Act of 1933, as amended, or an exemption therefrom. This press release is being given (together with any further information which may be provided to the recipient) on the condition that it is for use by the recipient for information purposes only (and not for the evaluation of any investment,

acquisition, disposal or any other transaction). Any failure to comply with these restrictions may constitute a violation of applicable securities laws.

The companies in which Takeda directly and indirectly owns investments are separate entities. In this press release, "Takeda" is sometimes used for convenience where references are made to Takeda and its subsidiaries in general. Likewise, the words "we", "us" and "our" are also used to refer to subsidiaries in general or to those who work for them. These expressions are also used where no useful purpose is served by identifying the particular company or companies.

Takeda Forward-Looking Statements

This press release and any materials distributed in connection with this press release may contain forward-looking statements, beliefs or opinions regarding Takeda's future business, future position and results of operations, including estimates, forecasts, targets and plans for Takeda. Without limitation, forward-looking statements often include words such as "targets", "plans", "believes", "hopes", "continues", "expects", "aims", "intends", "ensures", "will", "may", "should", "would", "could", "anticipates", "estimates", "projects" or similar expressions or the negative thereof. These forward-looking statements are based on assumptions about many important factors, including the following, which could cause actual results to differ materially from those expressed or implied by the forward-looking statements: the economic circumstances surrounding Takeda's global business, including general economic conditions in Japan and the United States; competitive pressures and developments; changes to applicable laws and regulations, including global health care reforms; challenges inherent in new product development, including uncertainty of clinical success and decisions of regulatory authorities and the timing thereof; uncertainty of commercial success for new and existing products; manufacturing difficulties or delays; fluctuations in interest and currency exchange rates; claims or concerns regarding the safety or efficacy of marketed products or product candidates; the impact of health crises, like the novel coronavirus pandemic, on Takeda and its customers and suppliers, including foreign governments in countries in which Takeda operates, or on other facets of its business; the timing and impact of post-merger integration efforts with acquired companies; the ability to divest assets that are not core to Takeda's operations and the timing of any such divestment(s); and other factors identified in Takeda's most recent Annual Report on Form 20-F and Takeda's other reports filed with the U.S. Securities and Exchange Commission, available on Takeda's website at: https://www.takeda.com/investors/sec-filings-and-security-reports/ or at www.sec.gov. Takeda does not undertake to update any of the forward-looking statements contained in this press release or any other forward-looking statements it may make, except as required by law or stock exchange rule. Past performance is not an indicator of future results and the results or statements of Takeda in this press release may not be indicative of, and are not an estimate, forecast, guarantee or projection of Takeda's future results.

Takeda Medical Information

This press release contains information about products that may not be available in all countries, or may be available under different trademarks, for different indications, in different dosages, or in different strengths. Nothing contained herein should be considered a solicitation, promotion or advertisement for any prescription drugs including the ones under development.

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