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News Release

Protagonist and Takeda Announce ASCO Plenary Presentation Highlighting Full 32-Week Results from Phase 3 VERIFY Study of Rusfertide, Showing Reductions in Phlebotomy, Improved Hematocrit Control in Polycythemia Vera

OSAKA, Japan, June 2, 2025 – Takeda (TSE:4502/NYSE:TAK) ("Takeda") and Protagonist Therapeutics, Inc. (NASDAQ:PTGX) announced on June 1, 2025 (CST), at American Society of Clinical Oncology (ASCO) Annual Meeting, detailed results from the Phase 3, randomized, placebo-controlled VERIFY study evaluating rusfertide in patients with polycythemia vera (PV), which met the primary and all key secondary endpoints. Please see the attached press release for details.

The topline results of this study were disclosed on March 3, 2025, in "Protagonist and Takeda Announce Positive Topline Results from Phase 3 VERIFY Study of Rusfertide in Patients with Polycythemia Vera".

The impact on Takeda's financial results for the fiscal year ending March 31, 2026 (FY2025), following the study results, is immaterial.

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Protagonist and Takeda Announce ASCO Plenary Presentation Highlighting Full 32-Week Results from Phase 3 VERIFY Study of Rusfertide, Showing Reductions in Phlebotomy, Improved Hematocrit Control in Polycythemia Vera

- ***Rusfertide plus current standard of care more than doubled clinical response rates across high- and low-risk PV groups, significantly reducing phlebotomy eligibility compared to placebo plus current standard of care, which was the primary endpoint***
- ***All key secondary endpoints met with statistical significance, including a nearly three-fold reduction in the proportion of patients requiring phlebotomy and a four-fold improvement in hematocrit control in rusfertide arm compared to placebo arm, as well as improvements in patient-reported outcomes***
- ***No serious adverse events considered related to rusfertide were reported***
- ***Rusfertide has received Orphan Drug designation and Fast Track designation from the U.S. FDA***

NEWARK, California, OSAKA, Japan and CAMBRIDGE, Massachusetts, June 1, 2025 – Protagonist Therapeutics, Inc. ("Protagonist") (NASDAQ:PTGX) and Takeda (TSE:4502/NYSE:TAK) announced detailed results from the Phase 3, randomized, placebo-controlled VERIFY study evaluating rusfertide in patients with polycythemia vera (PV), which met the primary and all key secondary endpoints. The data will be presented as a late-breaking oral presentation at the 61st American Society of Clinical Oncology (ASCO) Annual Meeting Plenary Session (LBA3) at 2:09 pm CDT today.

PV is characterized by overproduction of red blood cells (erythrocytosis), which may increase blood viscosity, or thickness, potentially resulting in life threatening thrombotic events such as stroke, deep vein thrombosis and pulmonary embolism. People with PV can experience burdensome symptoms, including severe fatigue, difficulty in concentrating, night sweats and pruritus, which may negatively impact their daily functioning and quality of life. Hematocrit is the ratio of red blood cells to total amount of blood in the body. Achieving and maintaining controlled hematocrit levels of <45% is the primary treatment goal in PV to prevent thrombotic events and alleviate symptoms, but many patients still experience uncontrolled hematocrit levels with current standard of care treatments.

Rusfertide, an investigational, first-in-class hepcidin mimetic peptide therapeutic, is under evaluation in the Phase 3 VERIFY study for its potential to regulate iron homeostasis and red blood cell production to control hematocrit levels in patients with PV. In the study, patients dependent on frequent phlebotomy, with or without treatment with cytoreductive therapy, were randomized to receive once-weekly rusfertide or placebo, as an add-on to current standard of care treatment.

"PV poses significant challenges for patients, including debilitating symptoms and the risk of serious thrombotic events, and hematocrit control is crucial to improving patient outcomes. The VERIFY study demonstrated that treatment with rusfertide controls hematocrit levels in phlebotomy-dependent patients, including patients receiving cytoreductive therapies," said Dr. Andrew T. Kuykendall, M.D., VERIFY Lead Investigator and Associate Member in the Department of Hematology at Moffitt Cancer Center. "These results suggest rusfertide has the potential to become part of the standard of care treatment for patients with PV."

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The study met its primary endpoint, which was the proportion of patients achieving a clinical response, defined as the absence of phlebotomy eligibility during study Weeks 20-32. Study results demonstrated 76.9% of patients treated with rusfertide plus current standard of care achieved a clinical response, compared to 32.9% in the placebo plus current standard of care group ($p<0.0001$).[1] The response observed in the rusfertide arm was consistent across subgroups, regardless of risk status or type of concurrent cytoreductive therapy.[1] In addition, all key secondary endpoints met statistical significance in favor of the rusfertide arm compared to the placebo arm in the VERIFY study, as follows:

- The mean number of phlebotomies was 0.5 phlebotomies per patient for those treated with rusfertide plus current standard of care compared to 1.8 phlebotomies per patient for those treated with placebo plus current standard of care during Weeks 0-32; ($p<0.0001$).[1]
    - Only 27% of patients treated with rusfertide plus current standard of care required phlebotomy between Weeks 0-32, compared to 78% of patients who received placebo plus current standard of care.
    - The mean number of phlebotomies during Weeks 0-32 in the rusfertide arm was reduced across subgroups, including risk status and use of concurrent cytoreductive therapy, versus the placebo arm.
- 62.6% of patients treated with rusfertide plus current standard of care maintained hematocrit levels below 45% versus 14.4% treated with placebo plus current standard of care ($p<0.0001$).[1]
- Rusfertide also showed statistically significant improvements in mean change from baseline to Week 32 in PROMIS Fatigue[2] ($p<0.03$) and the MFSAF Total Symptom Score[3] ($p<0.03$). Rusfertide is the first investigational therapy to prospectively demonstrate a statistically significant improvement in these patient-reported outcomes (PROs) of fatigue and symptom burden in patients with PV.[1]

Rusfertide was generally well tolerated. The majority of adverse events were low grade and non-serious and no serious adverse events considered related to rusfertide were reported. There was no evidence of increased risk of cancer in patients treated with rusfertide plus current standard of care compared to patients treated with placebo plus current standard of care at the time of the primary analysis. Cancer events were reported in one patient in the rusfertide arm (0.7%) and in seven patients in the placebo arm (4.8%). The most common treatment-emergent adverse events were localized injection site reactions (55.9%), anemia (15.9%) and fatigue (15.2%).[1]

“These findings underscore rusfertide’s potential as a first-in-class erythrocytosis-specific treatment for PV and validate more than a decade of scientific innovation originating from Protagonist’s peptide technology platform,” said Dinesh V. Patel, Ph.D., President and Chief Executive Officer at Protagonist. “We would like to thank all the patients, study staff and investigators for participating in the VERIFY study. We are pleased to partner with Takeda as we continue to advance rusfertide to potentially transform the standard of care in PV patients around the world.”

“These promising pivotal data strongly support rusfertide's potential benefit for a broad spectrum of patients with PV who may be receiving current standard of care therapies but not achieving adequate hematocrit control,” said Phuong Khanh (P.K.) Morrow, M.D., Head of the Oncology Therapeutic Area Unit (OTAU) at Takeda. “We look forward to receiving additional data from the VERIFY trial later this

year, advancing rusfertide towards regulatory approval and continuing our collaboration with Protagonist to bring this innovative therapy to patients."

Rusfertide has received Orphan Drug designation and Fast Track designation from the U.S. Food & Drug Administration (FDA).

Takeda Investor Conference Call and Webcast Details

Takeda will host an investor call regarding this update on **Sunday, June 1, 6-6:45 pm CDT/ 7-7:45 pm EDT / Monday, June 2, 08:00-08:45 (JST).**

The call will be held using the Zoom platform and Zoom simultaneous interpretation function. Kindly pre-register from the below link:
https://zoom.us/webinar/register/WN_rNp8tpIiRsemQRawBCDRMA#/registration

An on-demand replay will be made available on Takeda's website after the conclusion of the event.

Protagonist Investor Conference Call and Webcast Details

The dial-in numbers for Protagonist's investor update on **Monday, June 2nd at 5:00-6:00 am PDT/ 8:00-9:00 am EDT** are:

- US-based Investors: 1-877-300-8521
- International Investors: 1-412-317-6026
- Conference Call ID: 10199589

The webcast link for the event can be found here:
https://viavid.webcasts.com/starthere.jsp?ei=1718556&tp_key=360d3b714d

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 study (NCT05210790) is an ongoing, three-part, global, randomized, placebo-controlled study evaluating rusfertide in 293 patients with polycythemia vera over a 156-week period. The study is evaluating the efficacy and safety of once-weekly, subcutaneously self-administered rusfertide in patients with uncontrolled hematocrit who are phlebotomy-dependent despite current 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 study evaluating the efficacy and safety of rusfertide plus current standard of care versus placebo plus current standard of care and are now in the open-label portions of the study.

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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, an oral hepcidin program, and an 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 regulatory submissions. 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”, “forecasts”, “outlook” 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 and with respect to international trade relations; competitive pressures and developments; changes to applicable laws and regulations, including tax, tariff and other trade-related rules; 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; the success of our environmental sustainability efforts, in enabling us to reduce our greenhouse gas emissions or meet our other environmental goals; the extent to which our efforts to increase efficiency, productivity or cost-savings, such as the integration of digital technologies, including artificial intelligence, in our business or other initiatives to restructure our operations will lead to the expected benefits; 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 https://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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1. Kuykendall A et al. Results From VERIFY, a Phase 3, Double-Blind, Placebo (PBO)-Controlled Study of Rusfertide for Treatment of Polycythemia Vera (PV). Oral presentation at: American Society of Clinical Oncology (ASCO) Annual Meeting, June 1, 2025. Chicago, IL. LBA3.
2. PROMIS Fatigue Short Form 8a Total T-Score
3. MFSAF v4.0 Total Symptom Score 7