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News Release

Protagonist and Takeda Present Longer-Term Data at ASH 2025 Showing Rusfertide Delivers Durable Response and Hematocrit Control in Polycythemia Vera

OSAKA, Japan, December 8, 2025 – Takeda (TSE:4502/NYSE:TAK) ("Takeda") and Protagonist Therapeutics, Inc. (NASDAQ:PTGX) announced on December 6, 2025 (ET), that new 52-week results from the pivotal Phase 3 VERIFY study evaluating rusfertide in patients with polycythemia vera were presented in an oral presentation at the 67th American Society of Hematology Annual Meeting and Exposition. For further details, please refer to the attached press release.

The topline results of this study were announced on March 3, 2025, in "Protagonist and Takeda Announce Positive Topline Results from Phase 3 VERIFY Study of Rusfertide in Patients with Polycythemia Vera". In addition, "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" was announced on June 2, 2025.

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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News Release

Protagonist and Takeda Present Longer-Term Data at ASH 2025 Showing Rusfertide Delivers Durable Response and Hematocrit Control in Polycythemia Vera

- ***52-Week Results from the Phase 3 VERIFY Study of Rusfertide Demonstrated Sustained Hematocrit Control and Response, Defined by Absence of Phlebotomy Eligibility, with No New Safety Signals***
- ***These Data Build on Positive 32-Week Primary Analysis from VERIFY, Which Met its Primary Efficacy Endpoint and All Four Key Secondary Endpoints***
- ***Patients Crossing Over from Placebo to Rusfertide at 32 Weeks Achieved a Similar Response Rate to Those Initially Randomized to Rusfertide, with 77.9% Achieving Absence of Phlebotomy Eligibility Between Weeks 40-52***
- ***Four-Year Results from the Combined REVIVE and Long-Term Extension THRIVE Study Demonstrated a 13-Fold Reduction in Annual Rate of Phlebotomies from Baseline***

NEWARK, California, OSAKA, Japan and CAMBRIDGE, Massachusetts, December 6, 2025 – Protagonist Therapeutics, Inc. ("Protagonist") (NASDAQ:PTGX) and Takeda (TSE:4502/NYSE:TAK) announce that new 52-week results from the pivotal Phase 3 VERIFY study evaluating rusfertide in patients with polycythemia vera (PV) will be presented in an oral presentation at the 67th American Society of Hematology (ASH) Annual Meeting and Exposition. These findings further reinforce rusfertide's efficacy and safety and demonstrate durability of response, with 61.9% of patients continuously treated with rusfertide maintaining absence of phlebotomy eligibility from baseline to Week 52.

"The 52-week data demonstrated the sustained efficacy of rusfertide, reducing the need for patients to receive phlebotomy while maintaining hematocrit control," said Dr. Andrew T. Kuykendall, M.D., VERIFY Lead Investigator and Associate Member in the Department of Hematology at Moffitt Cancer Center. "The 32-week VERIFY primary results were already promising, and this deeper understanding of the durability of response with rusfertide is critical to inform clinical decision-making for polycythemia vera. In totality, these findings, including the long-term extension data from THRIVE, reaffirm rusfertide as a potential new addition to the standard of care for patients with PV."

Achieving and maintaining controlled hematocrit (HCT) levels of <45% is the primary treatment goal in PV to prevent thrombotic events and help alleviate symptoms. However, many patients still experience uncontrolled hematocrit levels and burdensome symptoms with current standard of care treatments. The VERIFY study, designed to evaluate the efficacy and safety of rusfertide in patients with uncontrolled hematocrit who are phlebotomy-dependent despite receiving current standard of care treatment, met the primary endpoint and all four key secondary endpoints in its previously-reported 32-week primary analysis. During Part 1a (Weeks 0-32) of the VERIFY study, 293 patients were randomized to receive either rusfertide (147 patients) or placebo (146 patients), as an add-on to their current treatment. During Part 1b (Weeks 32-52), all participants were eligible to receive open-label rusfertide to evaluate the durability of the treatment response. 274 patients (94%) continued into Part 1b, and 267 patients (91%)

remained in the study through Week 52, with 254 continuing to receive rusfertide in Part 2 (Weeks 52-156).

Key findings at 52 Weeks include[1,2]:

Phlebotomy Eligibility

- 61.9% of patients treated with rusfertide plus current standard of care throughout Parts 1a and 1b of the study experienced a durable clinical response, defined as absence of phlebotomy eligibility.
- 84.1% of patients treated with rusfertide who experienced a clinical response in the Part 1a assessment window (Weeks 20-32) maintained their response.
- 77.9% of patients who crossed over from placebo to rusfertide at Week 32 for Part 1b experienced a clinical response during the Part 1b assessment window (Weeks 40-52).
- Median time to first phlebotomy was 16 Weeks in the placebo group, while median time to first phlebotomy was not reached in either the rusfertide group in Part 1a or 1b, or the placebo to rusfertide crossover group in Part 1b.

HCT Control

- Mean hematocrit remained <43% through Week 52 in patients treated with rusfertide throughout Part 1a and Part 1b and those who switched from placebo to rusfertide for Part 1b.
- Median time to first hematocrit ≥ 45% was 8.3 Weeks in the placebo group in Part 1a, while median time to first hematocrit ≥ 45% was not reached in the rusfertide group during Parts 1a or 1b.

Quality of Life Endpoints

- Patients treated with rusfertide in Parts 1a and 1b maintained improvements in patient reported outcomes as measured by PROMIS Fatigue SF-8a and MFSAF TSS7.

Rusfertide was generally well-tolerated through 52 Weeks of treatment. The most common treatment-emergent adverse events (AE) in rusfertide-treated patients were injection site reactions (47.4%), anemia (25.6%) and fatigue (19.6%), which were primarily grade 1 or 2. Serious AEs occurred in 8.1% of overall rusfertide-treated patients.

The durability of response and safety profile of rusfertide in patients with PV from the 52-week VERIFY data are further supported by the four-year analysis of 46 patients who continued from REVIVE to the long-term extension study, THRIVE.

The results show that after transitioning to THRIVE, continued treatment with rusfertide with or without cytoreductive therapy demonstrated consistent, long-term hematocrit control with a greater than 13-fold reduction in estimated annual therapeutic phlebotomy rate compared to baseline prior to study entry in REVIVE. Prior to study entry in REVIVE, the mean annualized phlebotomy rate (i.e., phlebotomy/year) for the 46 patients who eventually rolled over to THRIVE was 9.2 phlebotomies/year. The mean annualized phlebotomy rate during THRIVE was 0.7 phlebotomies/year.[3] Rusfertide's safety profile was consistent with prior observations.

"The totality of these data further demonstrates rusfertide's well tolerated safety profile and ability to deliver durable hematocrit control and clinical response as defined by absence of phlebotomy eligibility and support its potential to expand the treatment armamentarium for PV and positively impact the lives of patients with PV," said Arturo Molina, M.D., M.S., Chief Medical Officer at Protagonist. "We look

forward to continuing to work with our partner, Takeda, to prepare for submission of an NDA to the FDA."

"We are committed to making a difference for patients with PV who face serious risks from thrombotic events if they are unable to adequately control hematocrit levels with currently available treatment options," said Phuong Khanh (P.K.) Morrow, M.D., Head of the Oncology Therapeutic Area Unit at Takeda. "The comprehensive data presented at ASH, from the pivotal VERIFY and long-term THRIVE studies, strongly underscore the potential of rusfertide to provide a sustained response, addressing a critical unmet need in managing this chronic cancer. We are excited to advance rusfertide towards regulatory approval in collaboration with Protagonist, bringing us one step closer to improving the care of patients suffering from PV."

Rusfertide has received Breakthrough Therapy Designation, Orphan Drug Designation and Fast Track Designation from the U.S. Food & Drug Administration (FDA).

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, with treatment extension for participants who are continuing to derive benefit from rusfertide beyond the 156-week treatment 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.

About THRIVE

The THRIVE study (NCT06033586) is an ongoing, open-label extension study evaluating the long-term durability of response and safety profile of rusfertide in patients with polycythemia vera. The study includes 46 patients who previously participated in the Phase 2 REVIVE study (NCT04057040). Patients eligible to transition to the THRIVE study completed the open-label extension portion of REVIVE, ≥12 months of rusfertide therapy and had an end-of-treatment visit. THRIVE is designed to further assess the maintenance of hematocrit control, reduction in the need for therapeutic phlebotomy and overall safety of once-weekly, subcutaneous rusfertide over an additional two-year treatment period.

About Polycythemia Vera (PV)

Polycythemia vera (PV) is characterized by the overproduction of red blood cells (erythrocytosis), which increases blood viscosity, or thickness, that can result in life threatening thrombotic events such as stroke, deep vein thrombosis and pulmonary embolism. Hematocrit (HCT) is the ratio of red blood cells to total amount of blood in the body. Achieving and maintaining controlled HCT levels of <45% is the primary treatment goal in PV to prevent thrombotic events and alleviate burdensome symptoms, including severe fatigue, difficulty in concentrating, night sweats and pruritus.

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 (NDA) for icotrokinra submitted to the FDA in July and in the NDA submission for rusfertide expected by end of 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 Janssen Biotech, Inc., a Johnson & Johnson company, Inc. Following icotrokinra's joint discovery by Protagonist and Johnson & Johnson scientists pursuant to the companies' IL-23R collaboration, Protagonist was primarily responsible for development of icotrokinra through Phase 1, with Johnson & Johnson 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 in 2024 under which the Company remains primarily responsible for development through NDA filing. The Company also has a number of preclinical stage drug discovery programs addressing clinically and commercially validated targets, including IL-17 oral peptide antagonist PN-881, obesity triple agonist peptide PN-477, and the oral hepcidin program.

More information on Protagonist, its pipeline drug candidates and clinical studies can be found on the Company's website at https://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.

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1. Kuykendall A, et al. Rusfertide or Placebo Plus Current Standard of Care Therapy for Polycythemia Vera: Durability of Response and Safety Results Through Week 52 From the Randomized Controlled Phase 3 VERIFY Study. Oral presentation at: American Society of Hematology Annual Meeting, December 6, 2025. Orlando, FL. Presentation ID 81.
2. Kuykendall A, et al. Rusfertide or Placebo Plus Current Standard of Care Therapy for Polycythemia Vera: Durability of Response and Safety Results Through Week 52 From the Randomized Controlled Phase 3 VERIFY Study. Abstract accepted for oral presentation at: American Society of Hematology 2025 Annual Meeting. Orlando, FL. Abstract ID 81
3. Pemmaraju N, et al. Long-term rusfertide treatment in polycythemia vera: Initial results from the Phase 2 THRIVE extension study. Abstract accepted for poster presentation at: American Society of Hematology 2025 Annual Meeting. Orlando, FL. Abstract ID 3810.