Precigen ActoBio Announces Positive Topline Results from Phase 1b/2a Study of AG019 ActoBiotics™, A Novel Therapy Designed to Address the Underlying Cause of Type 1 Diabetes

June 10, 2021

- Primary analysis data presented at the Federation of Clinical Immunology Societies (FOCIS) 2021 Virtual Annual Meeting -

- Primary endpoint assessing safety and tolerability met for both Phase 1b monotherapy and Phase 2a combination therapy portions of study -

- AG019, as monotherapy and in combination with teplizumab, showed stabilization of C-peptide levels, a biomarker for T1D disease progression, and induced antigen-specific tolerance in conjunction with the reduction of disease-specific T cell responses -

- Clinical trial assessing the efficacy of prolonged treatment of oral AG019 planned -

GERMANTOWN, Md., June 10, 2021 /PRNewswire/ -- Precigen ActoBio, an innovative clinical-stage biotechnology company focused on a new class of microbe-based therapeutic agents and a wholly-owned subsidiary of Precigen, Inc. (Nasdaq: PGEN), today announced positive topline results for the ongoing Phase 1b/2a clinical study investigating AG019 ActoBiotics™ for the treatment of recent-onset type 1 diabetes (T1D) (clinical trial identifier: NCT03751007, EudraCT 2017-002871-24). Results from the primary analysis were presented at the Federation of Clinical Immunology Societies (FOCIS) 2021 Virtual Annual Meeting by Kevan Herold, MD, Professor of Immunobiology and of Medicine at the Yale University.

T1D is an autoimmune disease in which the immune system destroys insulin-producing beta cells in the pancreas, resulting in a blood glucose imbalance. There is no approved disease-modifying treatment for T1D, which is currently managed through lifestyle modification and diet combined with exogenous insulin. Replacement insulin therapy is associated with a variety of near- and long-term adverse events, as is failure to properly control glucose levels within a narrow range.

AG019 is formulated as an oral capsule of engineered *Lactococcus lactis* specifically modified to deliver autoantigen human proinsulin (hPINS) and the tolerance-enhancing cytokine human interleukin-10 (hIL-10) to the mucosal lining of the gastrointestinal tissues. Administration of AG019 is designed to induce specific regulatory T cells (Tregs) that could reduce or eliminate the destruction of insulin-producing cells, potentially stabilizing or improving insulin production.

The Phase 1b open-label portion of the study evaluates the safety and tolerability of AG019 as a monotherapy in adult (age 18-42) and adolescent (age 12-17) patients. The primary endpoint for assessing safety and tolerability is treatment-emerging adverse events (TEAEs) reported up to 6 months post treatment initiation. The Phase 2a double-blind portion of the study investigates the safety and tolerability of AG019, in combination with an investigational anti-CD3 monoclonal antibody, teplizumab (PRV-031).

The primary endpoint of both the Phase 1b AG019 monotherapy and the Phase 2a AG019 combination therapy was met. AG019 was well tolerated and safe when administered to adults and adolescents either as monotherapy or in combination with teplizumab. No serious adverse events (SAEs) were reported and no AG019 treatment discontinuation occurred due to TEAEs. No severe TEAEs were reported in patients treated with AG019 monotherapy. The TEAEs reported for both the mono- and combination therapy were mostly mild and sometimes moderate severity. The TEAEs reported in the combination cohorts are in line with the safety profile reported for teplizumab and no unexpected TEAEs were identified. In addition, pharmacokinetic analyses demonstrated localized intestinal delivery of AG019 and no systemic exposure of hPINS, hIL-10 and of AG019 bacteria in the blood of the patients, confirming the safety profile of AG019.

Key clinical results for pharmacodynamic and metabolic markers include:

Phase 1b oral AG019 monotherapy:

- **Dosing:** Patients who received a daily dose of oral AG019 monotherapy for 8 weeks were evaluated for pharmacodynamic and metabolic markers.
- **Clinical Activity*:** Following a single 8-week treatment cycle of oral AG019, 56% of adult patients (5 of 9) showed stabilization or increase of C-peptide levels during the first 6 months post treatment initiation (defined as responders[1]). The highest percentage of responders (58%, 7 of 12) was seen in patients 17 years and above, indicating a potential target

population for the monotherapy. A sustained treatment effect may be achieved by prolonging AG019 treatment, which could be examined in a subsequent clinical trial.

- **Mechanistic Data:** In an independent analysis performed in a subset of adult and adolescent patients by the Immune Tolerance Network (ITN), a leading independent research group sponsored by the US National Institutes of Health, AG019 monotherapy induced antigen-specific tolerance in conjunction with the reduction of disease-specific T cell responses 6 months post treatment initiation.
    - Preproinsulin (PPI)-specific CD8+ T cells in circulation were reduced in 87% of patients (7 of 8) at 3 months and in 83% of patients (5 of 6) at 6 months.
    - A trend towards a correlation between PPI-specific CD8+ T cells reduction and C-peptide preservation was observed at 6 months.
    - An increase in the frequency of PPI-specific memory Tregs was observed in 75% of adult patients (3 of 4) at 6 months and an increase of PPI-specific CD4+ Tr1 cells was observed in 100% of adult patients (4 of 4) at 3 months after treatment initiation. An increase in the frequency of PPI-specific memory Tregs was observed in 60% of adolescent patients (3 of 5) up to 3 months.
- Results indicated the potential of oral AG019 monotherapy to preserve insulin production in recent-onset T1D through its capacity to reduce autoreactive T cells and increase the frequency of memory Tregs to induce antigen-specific immune modulation.

Phase 2a AG019 combination therapy:

- **Dosing:** Patients who received a daily dose of oral AG019 monotherapy for 8 weeks in combination with daily intravenous infusions of teplizumab for 12 days were evaluated for pharmacodynamic and metabolic markers.
- **Clinical Activity*:** Following treatment with the combination of AG019 and teplizumab, 70% of adult patients (7 of 10) and 100% of adolescent patients (4 of 4) showed stabilization or increase of C-peptide levels at 6 months post treatment initiation (defined as responders[1]). 79% of all patients (11 of 14) showed stabilization of C-peptide levels at 6 months post treatment initiation. C-peptide levels of the responders for whom 12-month data is available (n=8) remained above placebo levels.
- **Mechanistic Data:** In an independent analysis performed in adult and a subset of adolescent patients by the ITN, the combination of AG019 and teplizumab showed the induction of antigen-specific tolerance in conjunction with reduction of disease-specific T cell responses for adult and adolescent patients 6 months post treatment initiation.
    - PPI-specific CD8+ T cells in circulation were reduced in 63% of patients (7 of 11) at 3 months and in 67% of patients (6 of 9) at 6 months post treatment initiation.
    - An increase in the frequency of PPI-specific CD4+ Tr1 cells was observed at 3 months in 40% of adult patients (2 of 5) (analysis of PPI-specific memory Tregs ongoing).
- The extent of these antigen-specific immune modulatory effects in the combination therapy patients is similar to what was seen in AG019 monotherapy patients indicating that this effect may be attributed to the single 8-week treatment cycle of oral AG019.

"The primary analysis shows that AG019 can be administered safely, either as a monotherapy or in combination with teplizumab and provides an opportunity for chronic treatment of T1D," said Kevan Herold, MD, Professor of Immunobiology and of Medicine at Yale University and Principal Investigator for the AG019 Phase 1b/2a clinical study. "The stabilization of C-peptide in the monotherapy with a single 8-week treatment cycle of AG019 is encouraging in addition to the synergistic effect observed between AG019 and teplizumab. There may be an opportunity for sustained treatment effect following prolonged AG019 treatment."

"We are encouraged by the Phase 1b/2a primary analysis results and the implications for the potential of AG019 as an easy-to-take oral monotherapy or combination therapy with teplizumab. The stabilization of C-peptide levels and induced antigen-specific tolerance in conjunction with the reduction of disease-specific T cell response suggest the ability of AG019 to modulate a patient's immune system in a precise, antigen-specific manner to address the underlying cause of T1D," said Pieter Rottiers, PhD, CEO of Precigen ActoBio. "We are excited about advancing AG019 to assess the efficacy of prolonged treatment of oral AG019."

* Per Protocol Analysis Set: All data from patients who received at least 75% of the scheduled doses of AG019 and at least one dose of teplizumab in the combination cohorts and had no major protocol deviations affecting the main pharmacodynamic endpoints at the time point of data collection.

About Type 1 Diabetes (T1D)
T1D is an autoimmune disease in which the immune system destroys insulin-producing beta cells in the pancreas, resulting in a blood glucose imbalance. There is no approved disease-modifying treatment for T1D, which is currently managed through lifestyle modification and diet combined with exogenous insulin. As of 2019, more than 463 million adults (20-79 years, diagnosed and undiagnosed) globally are living with diabetes with T1D estimated to account for 23 million to 46 million (5 to 10%) of all diabetes cases. Over 1.1 million below 20 years of age have T1D with an estimated 128,900, under age 20 years, expected to develop T1D worldwide annually.[2]

About Precigen ActoBio ™
Precigen ActoBio is a clinical stage biotechnology company and a wholly-owned subsidiary of Precigen (Nasdaq: PGEN) pioneering a new class of therapeutic agents created on the ActoBiotics™ platform. The ActoBiotics™ platform provides a new class of therapeutic agent, a unique delivery platform precisely tailored for specific disease modification, with the potential for superior efficacy and safety via local delivery directly to the relevant tissue. ActoBiotics are targeted, microbe-based, specifically designed agents that express and locally deliver potential disease-modifying therapeutics at disease sites including the intestine, the mouth and the nasopharynx, to treat a range of disorders. Precigen ActoBio has a strong R&D pipeline and

an extensive portfolio of candidates advancing toward clinical development across a number of potential indications. Learn more about Precigen ActoBio at www.precigen.com/actobio/.

Precigen: Advancing Medicine with Precision ™

Precigen (Nasdaq: PGEN) is a dedicated discovery and clinical stage biopharmaceutical company advancing the next generation of gene and cell therapies using precision technology to target urgent and intractable diseases in our core therapeutic areas of immuno-oncology, autoimmune disorders, and infectious diseases. Our technologies enable us to find innovative solutions for affordable biotherapeutics in a controlled manner. Precigen operates as an innovation engine progressing a preclinical and clinical pipeline of well-differentiated unique therapies toward clinical proof-of-concept and commercialization. For more information about Precigen, visit www.precigen.com or follow us on Twitter @Precigen and LinkedIn.

Cautionary Statement Regarding Forward-Looking Statements

Some of the statements made in this press release are forward-looking statements. These forward-looking statements are based upon Precigen's current expectations and projections about future events and generally relate to plans, objectives, and expectations for the development of Precigen's business and the business of Precigen ActoBio, including the timing and progress of preclinical and clinical trials and discovery programs, and the promise of their portfolio of therapies. Although management believes that the plans and objectives reflected in or suggested by these forward-looking statements are reasonable, all forward-looking statements involve risks and uncertainties, including the possibility that the timeline for clinical trials might be impacted by the COVID-19 pandemic, and actual future results may be materially different from the plans, objectives and expectations expressed in this press release. Precigen has no obligation to provide any updates to these forward-looking statements even if its expectations change. All forward-looking statements are expressly qualified in their entirety by this cautionary statement. For further information on potential risks and uncertainties, and other important factors, any of which could cause Precigen's actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in Precigen's most recent Annual Report on Form 10-K and subsequent reports filed with the Securities and Exchange Commission.

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References

[1] Greenbaum et al., *Diabetes* 2012

[2] International Diabetes Foundation, Diabetes Atlas Ninth Edition 2019. IDF website

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