Alkermes Presents New Data on ALKS 4230 at Society for Immunotherapy of Cancer's (SITC) 35th Anniversary Annual Meeting

November 9, 2020

- Subcutaneous Dosing of ALKS 4230 in ARTISTRY-2 Showed Desired Immune Response and Safety Profile Consistent With the Observed Effects of Intravenous ALKS 4230 -

- New Data From ARTISTRY-1 Trial Provide Additional Evidence of Therapeutic Potential of ALKS 4230 as Monotherapy and in Combination With Pembrolizumab in Multiple Tumor Types -

DUBLIN, Nov. 9, 2020 /PRNewswire/ -- Alkermes plc (Nasdaq: ALKS) today announced the presentation of new data from the ARTISTRY clinical development program for ALKS 4230, Alkermes' investigational engineered interleukin-2 (IL-2) variant immunotherapy, at the Society for Immunotherapy of Cancer's (SITC) 35th Anniversary Annual Meeting, being held virtually Nov. 11-14, 2020. The company will present preliminary safety, tolerability and pharmacokinetic/pharmacodynamic data from the dose-escalation stage of ARTISTRY-2, the ongoing phase 1/2 study evaluating ALKS 4230 administered subcutaneously (SC) either once-weekly or once-every-three-weeks. A detailed analysis of clinical responses observed in ovarian cancer patients and other new updates from ARTISTRY-1, the ongoing phase 1/2 study investigating ALKS 4230 administered intravenously (IV), will also be presented. Both studies are evaluating ALKS 4230 as a monotherapy and in combination with the PD-1 inhibitor pembrolizumab (KEYTRUDA®) in patients with heavily pretreated advanced solid tumors.

"Accumulating evidence across the ARTISTRY clinical program provides insight into ALKS 4230's potential as a novel treatment option, both as monotherapy in melanoma and in combination with pembrolizumab, for a number of tumor types that do not typically respond to current standards of care. The responses observed with the combination regimen in platinum-resistant ovarian cancer, triple negative breast cancer, and recently in cervical cancer, are encouraging signs of ALKS 4230's potential utility in these cancers," said Ira Winer, M.D., Ph.D., Associate Professor, Division of Gynecologic Oncology, Wayne State University and Karmanos Cancer Institute. "In addition, the data presented at SITC from ARTISTRY-2 in patients with advanced solid tumors showed a safety profile and immune response comparable to ALKS 4230 administered intravenously, indicating that ALKS 4230 may offer an alternate subcutaneous dosing option for patients."

"The ALKS 4230 subcutaneous dose-escalation data in heavily pretreated patients with certain solid tumors demonstrated expansion of tumor-killing CD8+ T cells and NK cells consistent with the expansion observed with intravenous dosing of ALKS 4230. These data support the potential for once-weekly or once-every-three-week subcutaneous dosing of ALKS 4230, for which we expect to identify our recommended phase 2 dose by year-end," said Craig Hopkinson, M.D., Chief Medical Officer and Executive Vice President of Research & Development at Alkermes. "Further, based on the durable complete and partial responses observed in the ARTISTRY-1 intravenous dosing study in tumor types with high unmet need and limited treatment options for patients, we are considering potential regulatory strategies that may support expeditious development paths in both monotherapy and combination settings."

The two posters are available on the SITC website at https://sitc.sitcancer.org/2020/abstracts/titles/. Highlights from the poster presentations, which reflect **data as of Sept. 29, 2020** unless otherwise noted, include:

Poster #671: Phase 1/2 Study of Subcutaneously Administered ALKS 4230, a Novel Engineered Cytokine, as Monotherapy and in Combination With Pembrolizumab, in Patients With Advanced Solid Tumors: ARTISTRY-2
The ongoing dose-escalation stage of ARTISTRY-2 is evaluating the safety and tolerability of ascending doses of SC ALKS 4230 administered either once-weekly (Q7) or once-every-three-weeks (Q21) as lead-in monotherapy for six weeks, followed by combination with pembrolizumab. The pharmacokinetic/pharmacodynamic (PK/PD) data presented include seven dose-escalation cohorts of SC ALKS 4230 (Q7: 0.3, 0.6, 1, 3 mg; Q21: 1, 3, 10 mg):

- ALKS 4230 was assessed in 43 heavily pretreated patients with refractory solid tumors. Of these, 30 patients completed the monotherapy lead-in portion of the study and initiated combination treatment with pembrolizumab.
- Treatment with SC ALKS 4230 resulted in a dose-dependent increase in circulating natural killer (NK) cells and CD8+ T cells, with an approximately 16-fold and 3-fold expansion, respectively, at the 3 mg Q7 dose. At the 10 mg Q21 dose there was an approximately 6-fold and 3-fold expansion in NK cells and CD8+ T cells, respectively. There was a minimal, non-dose-dependent change in regulatory T (T_{reg}) cells.
    - The NK and CD8+ T cell expansions observed for the 3 mg Q7 and 10 mg Q21 SC doses were equivalent or greater compared to the expansions observed in ARTISTRY-1 at the 3 µg/kg/day and 6 µg/kg/day IV doses of ALKS 4230, respectively.
    - Compared to the 6 µg/kg/day IV dose, the recommended phase 2 dose (RP2D) identified for ARTISTRY-1, the 3 mg and 10 mg doses of SC ALKS 4230 induced higher levels of interferon gamma, a cytokine that has been associated with antitumor efficacy in clinical studies.[1] Relative to IV ALKS 4230, SC ALKS 4230 induced a lower, transient upregulation of IL-6 concentrations.
    - ALKS 4230 at the SC doses studied showed a safety and tolerability profile consistent with the anticipated pharmacologic effects and what has been observed with IV ALKS 4230. The most commonly reported adverse

events (AEs) across the ARTISTRY-2 study were injection site reactions, fever, chills, fatigue, nausea and lymphopenia. One patient experienced dose-limiting AEs at the 10 mg Q21 dose (grade 3 nausea, vomiting, and fatigue). Following a dose reduction, the patient continued on study.

- Preliminary clinical benefit was observed, even in immunotherapy-pretreated patients. As of the data cutoff date, 11 patients had continued on therapy for more than 6 months.
- The maximum tolerated dose and the RP2D for SC ALKS 4230 have not yet been determined.

Poster #689: Clinical Outcomes of Ovarian Cancer Patients Treated With ALKS 4230, a Novel Engineered Cytokine, in Combination With Pembrolizumab: ARTISTRY-1 Trial

Data presented from the ongoing ARTISTRY-1 study focused on the subset of PD-1/L1 unapproved patients with progressive, resistant ovarian cancer who received ALKS 4230 administered intravenously in combination with pembrolizumab. These data provide an updated and more in-depth view of responses previously reported at the 2020 European Society for Medical Oncology (ESMO) Virtual Congress. In addition, new data on the effects of IV ALKS 4230 monotherapy on the tumor microenvironment (TME) and additional updates from other tumor types were presented.

- Of the 13 evaluable ovarian cancer patients in the PD-1/L1 unapproved cohort, five patients with platinum-resistant ovarian cancer experienced clinical benefit, both in terms of durability and deepening of response. As of the data cutoff date, these five patients remained on therapy for a range of approximately 5 to 21 months.
- Antitumor activity has also been observed in patients with certain other women's cancers who received IV ALKS 4230 in combination with pembrolizumab, including a durable immune partial response in triple negative breast cancer and a new partial response in cervical cancer.
- An analysis of paired biopsies taken from a melanoma patient who received the 6 µg/kg/day monotherapy dose of IV ALKS 4230 in the dose-escalation phase of ARTISTRY-1 showed an increase in tumor-infiltrating CD8+ T cells and an increase in PD-L1 expression in the TME. In addition, the ratio of CD8+ T cells to T_{reg} cells increased in this patient. High CD8+ T cell/T_{reg} cell ratios, independent of treatment type, have been reported to be associated with better prognosis among multiple tumor types, including ovarian tumors.[2] These data provide supporting evidence of ALKS 4230's immunostimulatory impact on the TME and provide rationale for combining ALKS 4230 with pembrolizumab in ovarian cancer patients.
- Among patients in the PD-1/L1 unapproved cohort, treatment-related AEs have been generally transient and manageable, with the majority being grade 1 or 2 in severity. The most commonly reported AEs in this cohort were chills, fever and nausea.
- Based on the durable and deepening responses observed with ALKS 4230 in combination with pembrolizumab in ovarian cancer, the company is planning a new prospective study to evaluate this combination regimen in platinum-resistant and bevacizumab-experienced ovarian cancer patients.

About ALKS 4230

ALKS 4230 is an investigational, novel, engineered fusion protein comprised of modified interleukin-2 (IL-2) and the high affinity IL-2 alpha receptor chain, designed to selectively expand tumor-killing immune cells while avoiding the activation of immunosuppressive cells by preferentially binding to the intermediate-affinity IL-2 receptor complex. The selectivity of ALKS 4230 is designed to leverage the proven antitumor effects of existing IL-2 therapy while mitigating certain limitations.

About the ARTISTRY Clinical Development Program

ARTISTRY is an Alkermes-sponsored clinical development program evaluating ALKS 4230 in patients with advanced solid tumors.

ARTISTRY-1 and ARTISTRY-2 are phase 1/2 studies evaluating the safety, tolerability, efficacy and pharmacokinetic and pharmacodynamic effects of ALKS 4230 in patients with refractory advanced solid tumors, in both monotherapy and combination settings with the PD-1 inhibitor pembrolizumab (KEYTRUDA®). In ARTISTRY-1, ALKS 4230 is administered as an intravenous infusion daily for five consecutive days. In ARTISTRY-2, ALKS 4230 is administered subcutaneously and is being evaluated with once-weekly and once-every-three-week dosing schedules.

ARTISTRY-3 is a phase 2 study evaluating the clinical and immunologic effects of ALKS 4230 monotherapy administered intravenously on the tumor microenvironment of a variety of advanced, malignant solid tumors.

About Alkermes

Alkermes plc is a fully integrated, global biopharmaceutical company developing innovative medicines in the fields of neuroscience and oncology. The company has a portfolio of proprietary commercial products focused on addiction and schizophrenia, and a pipeline of product candidates in development for schizophrenia, bipolar I disorder, neurodegenerative disorders, and cancer. Headquartered in Dublin, Ireland, Alkermes plc has an R&D center in Waltham, Massachusetts; a research and manufacturing facility in Athlone, Ireland; and a manufacturing facility in Wilmington, Ohio. For more information, please visit Alkermes' website at www.alkermes.com.

Note Regarding Forward-Looking Statements

Certain statements set forth in this press release constitute "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to, statements concerning: the potential therapeutic value of ALKS 4230 as a cancer immunotherapy when used as monotherapy or in combination across multiple tumor types; and the details and status of, and plans for, the clinical development of ALKS 4230, including the timing for identification of the recommended phase 2 dose of SC ALKS 4230 for ARTISTRY 2, potential regulatory strategies to support expeditious development paths of ALKS 4230 in monotherapy and combination settings, and the company's plans for a new study to evaluate ALKS 4230 in combination with pembrolizumab in platinum-resistant and bevacizumab-experienced ovarian cancer patients. You are cautioned that forward-looking statements are inherently uncertain. Although the company believes that such statements are based on reasonable assumptions within the bounds of its knowledge of its business and operations, the forward-looking statements are neither promises nor guarantees and they are necessarily subject to a high degree of uncertainty and risk. Actual results may differ materially from those expressed or

implied in the forward-looking statements due to various risks and uncertainties. These risks and uncertainties include, among others, whether ALKS 4230, as a monotherapy or in combination, could be shown to be unsafe or ineffective; whether preclinical results and data from ongoing clinical studies for ALKS 4230—whether as a monotherapy or in combination—will be predictive of future or final results from such studies, results of future clinical studies or real-world results; whether future clinical trials or future stages of ongoing clinical trials for ALKS 4230, as a monotherapy or in combination, will be initiated or completed on time or at all; changes in the cost, scope and duration of, and clinical trial operations for, development activities for ALKS 4230, including changes relating to the impact of the novel coronavirus (COVID-19) pandemic; and those risks and uncertainties described under the heading "Risk Factors" in the company's Annual Report on Form 10-K for the year ended Dec. 31, 2019, the company's Quarterly Report on Form 10-Q for the quarter ended June 30, 2020 and in subsequent filings made by the company with the U.S. Securities and Exchange Commission (SEC), which are available on the SEC's website at www.sec.gov. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. Except as required by law, the company disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this press release.

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1. Ni L, Lu J. Cancer Med. 2018;7:4509–4516. 10.1002
2. Sato E, et al. Proc Natl Acad Sci U S A. 2005;102(51):18538-18543

Alkermes Contacts:
For Investors: Sandy Coombs, +1 781 609 6377
For Media: Sourojit Bhowmick, Ph.D.,+1 781 609 6397

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