Taiho Oncology and Servier Announce Positive Results from LONSURF® (trifluridine/tipiracil) Study Presented at ESMO 2018 Congress and Published in The Lancet Oncology

Results from TAGS Trial Meets Primary and Secondary Endpoints Demonstrating Prolonged Overall Survival in Patients with Metastatic Gastric/Gastroesophageal Junction (GEJ) Adenocarcinoma

PRINCETON, N.J., October 21, 2018 – Taiho Oncology, Inc. (U.S.), a subsidiary of Taiho Pharmaceutical Co., Ltd. (Japan) and Servier jointly announced today the clinical data from the pivotal Phase III (TAGS) trial evaluating LONSURF® (trifluridine/tipiracil, TAS-102) versus placebo and best supportive care in patients with heavily pretreated metastatic gastric/gastroesophageal junction (GEJ) cancers who have progressed or are intolerant to previous lines of therapy. The trial met its primary endpoint of prolonged overall survival (OS) and secondary endpoint measures of progression-free survival (PFS), as well as continued to demonstrate LONSURF's predictable safety and tolerability profile. *TAGS, a phase 3, randomised, double-blind study of trifluridine/tipiracil (TAS-102) versus placebo in patients with refractory metastatic gastric cancer (Abstract #LBA25)*, data were presented by Hendrik-Tobias Arkenau, MD, PhD, from the Sarah Cannon Research Institute (UK) at the ESMO 2018 Congress in Munich, Germany during an oral session on Sunday, October 21 at 11:10 AM CEST. The study results were simultaneously published in *The Lancet Oncology.*

"Patients with metastatic gastric/GEJ adenocarcinoma currently have limited treatment options after first and second line therapies have failed," said Arkenau, founding medical director of Sarah Cannon Research Institute UK and investigator on the TAGS trial. "We are pleased to present new data that demonstrate the overall survival clinical benefit of LONSURF (trifluridine/tipiracil) in metastatic gastric or gastroesophageal junction cancer."

In the TAGS trial, patients treated with LONSURF showed a clinically meaningful and statistically significant improvement in OS compared with placebo, a 31 percent risk reduction of death (HR 0.69 one sided p=0.00029), which translated into a prolongation of median survival of 2.1 months (5.7 months for trifluridine/tipiracil versus 3.6 months for placebo). In addition, LONSURF demonstrated a statistically significant improvement in PFS and time to deterioration of ECOG performance status versus placebo, as well as a predictable and manageable safety profile consistent with that previously reported in patients with metastatic colorectal cancer.

"These results further expand the proven clinical benefit of LONSURF beyond metastatic colorectal cancer patients, to include metastatic gastric and GEJ cancer patients. This represents a significant milestone in our efforts to expand the body of

evidence for trifluridine/tipiracil in the treatment of GI cancers," said Martin J. Birkhofer, MD, senior vice president and Chief Medical Officer, Taiho Oncology, Inc. "With so few options available for patients living with metastatic gastric cancer, we're excited by these results and the potential to make a difference in the lives of people who continue to struggle with this devastating disease."

LONSURF is currently indicated in the United States for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy and, if RAS wild-type, an anti-EGFR therapy.[1]

About TAGS

TAGS (***TA***S-102 ***G***astric ***S***tudy) is a Taiho-sponsored pivotal Phase III, multinational, randomized, double-blind study evaluating trifluridine/tipiracil, also known as TAS-102, plus best supportive care (BSC) versus placebo plus BSC in patients with metastatic gastric cancer, including gastro esophageal junction cancer, refractory to standard treatments. The primary endpoint in the TAGS trial is overall survival (OS), and the main secondary endpoint measures include progression-free survival (PFS), and safety and tolerability, as well as quality of life.

TAGS enrolled 507 adult patients with metastatic gastric cancer who had previously received at least two prior regimens for advanced disease. The study was conducted in Japan, the United States, the European Union, Russia, Belarus, Israel, and Turkey.

For more information on TAGS, please visit www.ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT02500043). The ClinicalTrials.gov Identifier is NCT02500043.

About Metastatic Gastric Cancer

Gastric cancer, also known as stomach cancer, is a disease in which malignant cells form in the lining of the stomach. It is the fifth most common cancer worldwide and the third most common cause of cancer-related death (after lung and liver cancer), with an estimated 723,000 deaths annually.[2] Approximately 50 percent of patients with gastric cancer have advanced disease at the time of diagnosis.[3]

Standard chemotherapy regimens for advanced gastric cancer include fluoropyrimidines, platinum derivatives, and taxanes (with ramucirumab), or irinotecan. The addition of trastuzumab to chemotherapy is standard of care for patients with HER2-neu-positive advanced gastric cancer. However, after failure of first- and second-line therapies, standard third-line treatments are limited.

About LONSURF

LONSURF (trifluridine/tipiracil) is an oral anticancer drug, which utilizes the combination of trifluridine (FTD) and tipiracil (TPI), whose dual mechanism of action is designed to maintain clinical activity and differs from conventional fluoropyrimidines. FTD is an antineoplastic nucleoside analogue, which is incorporated directly into the DNA, thereby interfering with the function of DNA. The blood concentration of FTD is maintained via TPI, which is an inhibitor of the FTD-degrading enzyme, thymidine phosphorylase.

In Japan, Taiho Pharmaceutical has been marketing LONSURF for the treatment of unresectable advanced or recurrent colorectal cancer since 2014. In the United States, beginning in 2015, Taiho Oncology, Inc., a U.S. subsidiary of Taiho Pharmaceutical, began marketing the drug for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy. In June 2015, Taiho Pharmaceutical and Servier entered into an exclusive license agreement for the co-development and commercialization of LONSURF in Europe and other countries outside of the United States, Canada, Mexico and Asia. In parts of Asia outside of Japan, Taiho Pharmaceutical's business partner TYY Biopharm launched LONSURF in Taiwan in July 2018, and Jeil Pharmaceutical is preparing to bring the drug to market in South Korea.

As of October 2018, LONSURF has been approved as a treatment for advanced mCRC in 60 countries and regions worldwide.

Indications and Use[9]
LONSURF is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor, indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

Important Safety Information[9]

LONSURF may cause serious side effects, including:

- **Low blood counts.** Low blood counts are common with LONSURF and can sometimes be severe and life-threatening. LONSURF can cause a decrease in your white blood cells, red blood cells, and platelets. Low white blood cells can make you more likely to get serious infections that could lead to death. Your healthcare provider should do blood tests before you receive LONSURF, at day 15 during treatment with LONSURF, and as needed to check your blood cell counts. Your healthcare provider may lower your dose of LONSURF or stop LONSURF if you have low white blood cell or platelet counts

Tell your healthcare provider right away if you get any of the following signs and symptoms of infection during treatment with LONSURF: fever, chills, or body aches.

Before taking LONSURF, tell your healthcare provider about all of your medical conditions, including if you:

- Have kidney or liver problems
- Are pregnant or plan to become pregnant. LONSURF can harm your unborn baby

    - **Females** who can become pregnant should use effective birth control during treatment with LONSURF. Tell your healthcare provider immediately if you become pregnant
    - **Males**, while on treatment and for 3 months after your last dose of LONSURF, you should use a condom during sex with female partners who are able to become pregnant. Tell your healthcare provider right away if your partner becomes pregnant while you are taking LONSURF
- Are breast-feeding or plan to breast-feed. It is not known if LONSURF passes into your breast milk. Do not breast-feed during treatment with LONSURF and for 1 day after your last dose of LONSURF

Tell your healthcare provider about all the prescription and over-the-counter medicines, vitamins, and herbal supplements you take.

The **most common side effects** with LONSURF include tiredness, nausea, decreased appetite, diarrhea, vomiting, abdominal pain, and fever.

Tell your doctor if you have nausea, vomiting, or diarrhea that is severe or that does not go away.

These are not all of the possible side effects of LONSURF. For more information, ask your healthcare provider. Call your doctor for medical advice about side effects.

Please see full US Prescribing Information.
www.taihooncology.com/us/prescribing-information.pdf

About Taiho Oncology, Inc. (U.S.)
Taiho Oncology, Inc., a subsidiary of Taiho Pharmaceutical Co., Ltd. and Otsuka Holdings Co., Ltd., has established a world class clinical development organization that works urgently to develop innovative cancer treatments and has built a commercial business in the U.S. Taiho has an oral oncology pipeline consisting of both novel antimetabolic agents and selectively targeted agents. Advanced technology, dedicated researchers, and state of the art facilities are helping us to define the way the world treats cancer. It's our work; it's our passion; it's our legacy.

For more information about Taiho Oncology, please visit:
https://www.taihooncology.com.

About Taiho Pharmaceutical Co., Ltd. (Japan)
Taiho Pharmaceutical, a subsidiary of Otsuka Holdings Co., Ltd., is an R&D-driven specialty pharma focusing on the three fields of oncology, allergy and immunology, and urology. Its corporate philosophy takes the form of a pledge: "We strive to improve human health and contribute to a society enriched by smiles." In the field of oncology in particular, Taiho Pharmaceutical is known as a leading company in Japan for developing innovative medicines for the treatment of cancer, a reputation that is rapidly expanding through their extensive global R&D efforts. In areas other than oncology, as well, the company creates and markets quality products that effectively treat medical conditions and can help improve people's quality of life. Always putting customers first,

Taiho Pharmaceutical also aims to offer consumer healthcare products that support people's efforts to lead fulfilling and rewarding lives.

For more information about Taiho Pharmaceutical, please visit: https://www.taiho.co.jp/en/.

About Otsuka Holdings Co., Ltd. (Japan)
The Otsuka group of companies is a total-healthcare enterprise that aims to contribute to the health of people around world under the corporate philosophy, “Otsuka-people creating new products for better health worldwide.”

Healthcare is broadly and holistically addressed through the two main pillars – the pharmaceutical business for the diagnosis and treatment of diseases and the nutraceutical[*1] business to support the maintenance and promotion of everyday health. Our 46,000[*2] employees across 183 companies in 28 countries and regions take on challenges across various fields and themes to help fulfill the universal wish of people to be healthy. Our pursuit of these challenges is motivated by the Otsuka’ s corporate culture, articulated as “Ryukan-godo” (by sweat we recognize the way), “Jissho” (actualization) and “Sozosei” (creativity), and fostered by successive generations of Otsuka leaders. By striving to provide unique products and services, we seek to achieve sustainable growth and be an indispensable contributor to the world.

For more information, please visit the company's website at https://www.otsuka.com/en/.

*1. Nutraceuticals: nutrition + pharmaceuticals *2. As of end of December 2017

About Servier

Servier is an international pharmaceutical company governed by a non-profit foundation, with its headquarters in France (Suresnes). With a strong international presence in 149 countries and a turnover of 4.152 billion euros in 2017, Servier employs 21,700 people worldwide. Entirely independent, the Group reinvests 25% of its turnover (excluding generic drugs) in research and development and uses all its profits for development. Corporate growth is driven by Servier’s constant search for innovation in five areas of excellence: cardiovascular, immune-inflammatory and neuropsychiatric diseases, cancer and diabetes, as well as by its activities in high-quality generic drugs. Servier also offers eHealth solutions beyond drug development.

Becoming a key player in oncology is part of Servier’s long-term strategy. Currently, there are twelve molecular entities in clinical development in this area, targeting gastro-intestinal and lung cancers and other solid tumors, as well as various leukemias and lymphomas. This portfolio of innovative cancer treatments is being developed with partners worldwide, and covers different cancer hallmarks and modalities, including cytotoxics, proapoptotics, targeted therapies, to deliver life-changing medicines to patients.

For more information about Servier, please visit www.servier.com.

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[1] LONSURF [US prescribing information]; Princeton, NJ: Taiho Oncology, Inc.; 2017. 2017.
[2] Ferlay J, Soerjomataram I, Dikshit R, et al. *Int J Cancer*. 2015;136:E359-86.
[3] National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. *Gastric cancer*. Version 2.2018. http://www.nccn.org. Accessed June 2018.