Media Release

Japan becomes the first country to approve Roche's personalised medicine Rozlytrek

- **First tumour-agnostic medicine approved in Japan for adult and paediatric patients with NTRK fusion-positive advanced recurrent solid tumours**
- **Approval supported by the data mainly from the pivotal Phase II STARTRK-2 study showing that Rozlytrek shrank tumours in more than half of people with NTRK fusion-positive solid tumours, across 10 different tumour types, including those with central nervous system metastases**
- **Rozlytrek is also undergoing review in Japan for the treatment of ROS1 fusion-positive non-small cell lung cancer**

Basel, 18 June 2019 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that Japan's Ministry of Health, Labour and Welfare (MHLW) has approved Rozlytrek® (entrectinib) for the treatment of adult and paediatric patients with neurotrophic tyrosine receptor kinase (NTRK) fusion-positive, advanced recurrent solid tumours. Rozlytrek is the first tumour-agnostic medicine to be approved in Japan that targets NTRK gene fusions, which have been identified in a range of hard-to-treat solid tumour types, including pancreatic, thyroid, salivary gland, breast, colorectal, and lung.[1] It has been granted Sakigake designation and orphan drug designation by the MHLW.[2]

Rozlytrek is also undergoing regulatory review in Japan for the treatment of people with ROS1 fusion-positive locally advanced or metastatic non-small cell lung cancer (NSCLC).[2]

"Today's approval of Rozlytrek represents a new chapter in personalised healthcare, applying advanced diagnostics to deliver precision medicines that target cancers based on their molecular drivers instead of their location in the body," said Sandra Horning, MD, Roche's Chief Medical Officer and Head of Global Product Development. "We are proud to be at the forefront of personalised medicine with this novel treatment approach, and we look forward to working with regulatory agencies around the world to bring Rozlytrek to more patients with NTRK fusion-positive cancer, as well as to those with ROS1 fusion-positive NSCLC, as soon as possible."

The data package for this first approval of Rozlytrek includes the pivotal Phase II STARTRK-2, Phase I STARTRK-1 and Phase I ALKA-372-001 trials, as well as data from the Phase I/II STARTRK-NG study in paediatric patients. Results showed:

- In the pivotal Phase II STARTRK-2 study, Rozlytrek shrank tumours in more than half (objective response rate [ORR] = 56.9 percent) of people with NTRK fusion-positive solid tumours. Objective responses to Rozlytrek were seen across 10 different solid tumour types (median duration of response [DoR] = 10.4 months), including in people with and without CNS metastases at baseline.[2]

    - Importantly, Rozlytrek also shrank tumours that had spread to the brain in more than half of people (intracranial response [IC] ORR = 50.0 percent).[2]
- In the STARTRK-NG study, Rozlytrek shrank tumours also in children and adolescents who had NTRK fusion-positive solid tumours including the patients with primary CNS tumours.[3]
- The most commonly reported adverse reactions include constipation, altered sense of taste (dysgeusia), diarrhoea, dizziness, fatigue, swelling (oedema), weight increase, anaemia, blood creatinine increase, shortness of breath (dyspnea), and nausea.[2]

Biomarker testing for NTRK gene fusions is the only way to identify people who may be eligible for treatment with Rozlytrek. Roche is leveraging its expertise in developing personalised medicines and advanced diagnostics, in conjunction with Foundation Medicine, to help identify people with NTRK gene fusions using a companion diagnostic that is undergoing review.

About the supporting data

The data package for this approval includes the pivotal Phase II STARTRK-2, Phase I STARTRK-1 and Phase I ALKA-372-001 trials. In addition, data from the Phase I/II STARTRK-NG study in paediatric patients were also included in the submission. The studies enrolled people across 15 countries and more than 150 clinical trial sites. Tumour types evaluated in the studies included breast, cholangiocarcinoma, colorectal, gynaecological, neuroendocrine, non-small cell lung, salivary gland, pancreatic, sarcoma and thyroid cancers.[1,2]

- **STARTRK-2** is a Phase II, global, multicentre, open-label basket study in people with solid tumours that harbour an NTRK1/2/3, ROS1 or ALK-positive gene fusion. The primary endpoint is objective response rate (ORR), and duration of response (DoR) is a secondary endpoint. Other secondary outcome measures include time to response, clinical benefit rate, intracranial tumour response, progression-free survival (PFS), central nervous system (CNS) PFS and overall survival (OS).[4]
- **STARTRK-1** is a Phase I, multicentre, open-label dose escalation study of a daily continuous dosing schedule in people with solid tumours with NTRK1/2/3, ROS1 or ALK gene fusions in the US and South Korea. The trial assessed the safety and tolerability of Rozlytrek via a standard dose escalation scheme and determined the recommended Phase II dose.[5]
- **ALKA-372-001** is Phase I, multicentre, open-label dose escalation study of an intermittent and continuous Rozlytrek dosing schedule in people with advanced or metastatic solid tumours with TRKA/B/C, ROS1 or ALK gene fusions in Italy.[2]
- **STARTRK-NG** is a Phase I/II dose-escalation and expansion study evaluating the safety and efficacy of Rozlytrek in children and adolescent patients with no curative first-line treatment option, recurrent or refractory extracranial solid tumours or primary CNS tumours, with or without TRK, ROS1 or ALK fusions.[3]

About NTRK fusion-positive cancer
Neurotrophic tyrosine receptor kinase (NTRK) fusion-positive cancer occurs when the NTRK1/2/3 genes fuse with other genes, resulting in altered TRK proteins (TRKA/TRKB/TRKC) that can activate signaling pathways involved in proliferation of certain types of cancer. NTRK gene fusions are tumour-agnostic, meaning they are present in tumours irrespective of site of origin. These fusions have been identified in a broad range of solid tumour types, including breast, cholangiocarcinoma, colorectal, gynaecological, neuroendocrine, non-small cell lung, salivary gland, pancreatic, sarcoma and thyroid cancers.[1]

About Rozlytrek
Rozlytrek (RXDX-101) is an oral medicine for the treatment of locally advanced or metastatic solid tumours that harbour NTRK1/2/3, as well as in development for the treatment of ROS1 gene fusions. It is a selective tyrosine kinase inhibitor designed to inhibit the kinase activity of the TRK A/B/C and ROS1 proteins, whose activating fusions drive proliferation in certain types of cancer.[6,7] Rozlytrek can block ROS1 and NTRK kinase activity and may result in the death of cancer cells with ROS1 or NTRK gene fusions.[6,7]

Rozlytrek has been granted Priority Review by the FDA for the treatment of NTRK fusion-positive, locally advanced or metastatic solid tumours in adult and paediatric patients who have either progressed following prior therapies or as an initial therapy when there are no acceptable standard therapies, and for the treatment of people with metastatic, ROS1 fusion-positive NSCLC. It has also been granted Priority Medicines (PRIME) designation by the European Medicines Agency (EMA) and Sakigake designation and orphan drug designation by MHLW.[2]

About Roche
Roche is a global pioneer in pharmaceuticals and diagnostics focused on advancing science to improve people's lives. The combined strengths of pharmaceuticals and diagnostics under one roof have made Roche the leader in personalised healthcare – a strategy that aims to fit the right treatment to each patient in the best way possible.

Roche is the world's largest biotech company, with truly differentiated medicines in oncology, immunology, infectious diseases, ophthalmology and diseases of the central nervous system. Roche is also the world leader in in vitro diagnostics and tissue-based cancer diagnostics, and a frontrunner in diabetes management. Founded in 1896, Roche continues to search for better ways to prevent, diagnose and treat diseases and make a sustainable contribution to society. The company also aims to improve patient access to medical innovations by working with all relevant stakeholders. Thirty medicines developed by Roche are included in the World Health Organization Model Lists of Essential Medicines, among them life-saving antibiotics, antimalarials and cancer medicines. Moreover, for the tenth consecutive year, Roche has been recognised as the most sustainable company in the Pharmaceuticals Industry by the Dow Jones Sustainability Indices (DJSI).

The Roche Group, headquartered in Basel, Switzerland, is active in over 100 countries and in 2018 employed about 94,000 people worldwide. In 2018, Roche invested CHF 11 billion in R&D and posted sales of CHF 56.8 billion. Genentech, in the United States, is a wholly owned member of the Roche Group. Roche is the majority shareholder in Chugai Pharmaceutical, Japan. For more information, please visit www.roche.com.

References

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