Media Release

FDA grants Priority Review to Roche's personalised medicine entrectinib

Basel, 19 February 2019 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the US Food and Drug Administration (FDA) has accepted the company's New Drug Applications (NDAs) and granted Priority Review for entrectinib for the treatment of adult and paediatric patients with neurotrophic tropomyosin receptor kinase (NTRK) fusion-positive, locally advanced or metastatic solid tumours 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-positive non-small cell lung cancer (NSCLC). These NDAs are based on results from the integrated analysis of the pivotal Phase II STARTRK-2, Phase I STARTRK-1 and Phase I ALKA-372-001 trials, and data from the Phase I/Ib STARTRK-NG study. The FDA is expected to make a decision on approval by 18 August 2019.

"Entrectinib represents a unique approach to cancer treatment that can potentially target a range of hard-to-treat and rare NTRK fusion-positive tumours regardless of their site of origin, as well as treat ROS1-positive non-small cell lung cancer," said Sandra Horning, MD, Roche's Chief Medical Officer and Head of Global Product Development. "By combining comprehensive genomic profiling with actionable targeted therapies, like entrectinib, we are advancing our personalised healthcare goal to find the right treatment for each patient. We are working closely with the FDA to make this potential new option available as soon as possible."

The FDA grants Priority Review to medicines determined to have the potential to provide significant improvements in the treatment, prevention or diagnosis of a serious disease. Entrectinib was also granted Breakthrough Therapy Designation (BTD) by the US Food and Drug Administration (FDA); Priority Medicines (PRIME) designation by the European Medicines Agency (EMA); and Sakigake designation by the Japanese health authorities 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 have no acceptable standard therapies.[1] BTD is designed to expedite the development and review of medicines intended to treat serious or life-threatening diseases and to help ensure people have access to them through FDA approval as soon as possible.

Roche is leveraging its expertise in developing personalised medicines and advanced diagnostics, in conjunction with Foundation Medicine, to develop a companion diagnostic that will help identify people with ROS1 and NTRK gene fusions.

About the integrated analysis
The integrated analysis included data from 53 people with ROS1-activating gene fusions and 54 people with locally advanced or metastatic NTRK fusion-positive solid tumours (10 tumour types, >19 histopathologies) from the Phase II STARTRK-2, Phase I STARTRK-1 and Phase I ALKA-372-001 trials.[2,3] In addition, data from the Phase I/Ib STARTRK-NG study in paediatric patients were also included in the NDAs. The studies enrolled people across 15 countries and more than 150 clinical trial sites.[2,3] Tumour types evaluated in the

studies to date included breast, cholangiocarcinoma, colorectal, gynaecological, neuroendocrine, non-small cell lung, salivary gland, pancreatic, sarcoma and thyroid cancers.[3]

- **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.[4] The primary endpoint is objective response rate (ORR), and duration of response (DoR) is a secondary endpoint.[4] 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.[5] The trial assessed the safety and tolerability of entrectinib 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 entrectinib dosing schedule in people with advanced or metastatic solid tumours with TRKA/B/C, ROS1 or ALK gene fusions in Italy.[1]
- **STARTRK-NG** is a Phase I/II dose-escalation and expansion study evaluating the safety and efficacy of entrectinib 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.[6]

Results from the integrated analysis showed entrectinib shrank tumours (ORR) in more than half (57.4 percent) of people with NTRK fusion-positive solid tumours. [3] Objective responses to entrectinib were seen across 10 different solid tumour types (median DoR = 10.4 months), including in people with and without CNS metastases at baseline.[3] In these studies, entrectinib shrank tumours that had spread to the brain in more than half of people (intracranial response [IC ORR] = 54.5 percent), with more than a quarter of these people having a complete response.[3]

Entrectinib shrank tumours in 77.4 percent of people with locally advanced or metastatic ROS1-positive NSCLC.[2] In addition, entrectinib demonstrated a durable response of more than two years (median DoR = 24.6 months).[2] Importantly, entrectinib was shown to shrink intracranial tumours in more than half of people with CNS metastases at baseline (IC ORR = 55.0 percent).[2]

The safety profile of entrectinib was consistent with that seen in previous analyses.[2,3] The most commonly reported adverse reactions included fatigue, constipation, altered sense of taste (dysgeusia), swelling (edema), dizziness, diarrhea, nausea, nervous system disorders (dysesthesia), shortness of breath (dyspnea), pain, anemia, cognitive disorders, weight increased, vomiting, cough, blood creatinine increase, joint pain (arthralgia), fever (pyrexia), and muscle pain (myalgia).[2,3]

About entrectinib

Entrectinib (RXDX-101) is an investigational, oral medicine in development for the treatment of locally advanced or metastatic solid tumours that harbour NTRK1/2/3 or 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.[7,8] Entrectinib can block ROS1 and NTRK

kinase activity and may result in the death of cancer cells with ROS1 or NTRK gene fusions.[7,8] Entrectinib is being investigated across a range of solid tumour types, including breast, cholangiocarcinoma, colorectal, gynaecological, neuroendocrine, non-small cell lung, salivary gland, pancreatic, sarcoma and thyroid cancers.[1,4-6]

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.[3] There is a high unmet medical need for treatments for people with life-threatening and hard-to-treat NTRK fusion-positive tumours.

About ROS1-positive NSCLC
ROS1 is a tyrosine kinase, which plays a role in controlling how cells grow and proliferate. When a ROS1 gene fusion occurs, cancer cells grow and proliferate in an uncontrolled manner. Blocking this abnormal signalling can cause tumour cells to shrink or die.[9]

ROS1 gene fusions account for 1-2% of NSCLC.[9] Lung cancer is the leading cause of cancer-related death across the world.[10] Each year, more than one and a half million people die as a result of the disease globally, equating to more than 4,000 deaths every day.[10] NSCLC is the most common type of lung cancer and accounts for 85% of all lung cancer diagnoses.[11] While the ROS1 gene fusion can be found in any patient with NSCLC, young never-smokers with NSCLC have the highest incidence of ROS1 gene fusions.[9]

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.

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