Media Release

CHMP recommends EU approval of Roche's Rozlytrek for people with NTRK fusion-positive solid tumours and for people with ROS1-positive, advanced non-small cell lung cancer

- **Rozlytrek has shown durable responses across multiple tumour types, including cancer that has spread to the brain, and could become Roche's first tumour-agnostic therapy in Europe**

Basel, 29 May 2020 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion under conditional marketing authorisation for Rozlytrek® (entrectinib) for the treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have not received a prior NTRK inhibitor, who have no satisfactory treatment options. The CHMP has also recommended Rozlytrek for the treatment of adults with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors.[1]

"Once approved, Rozlytrek could become Roche's first tumour-agnostic therapy in Europe," said Levi Garraway, M.D., Ph.D., Roche's Chief Medical Officer and Head of Global Product Development. "This milestone therefore represents additional progress in personalised healthcare. Based on genomic testing, Rozlytrek provides an effective first-line treatment for many people whose cancers harbour NTRK or ROS1 gene fusions, including tumours that have progressed to the brain."

The positive CHMP opinion is 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/II STARTRK-NG study. Results showed:

- Rozlytrek shrank tumours in more than half of people with NTRK fusion-positive, locally advanced or metastatic solid tumours (overall response rate [ORR]= 63.5%; N=74), and objective responses were observed across 14 tumour types (median duration of response [DoR] = 12.9 months [9.3 months – not reached], N=21 out of 47).[2]
- In ROS1-positive, advanced NSCLC, Rozlytrek shrank tumours in 73.4% of people with the disease (ORR; N=94 with 12 months follow up), with a median DoR of 16.5 months (14.6 - 28.6 months). In a group of 161 patients with 6 months follow up, including 29% of patients with central nervous system (CNS) metastases at baseline, ORR was observed to be 67.1%.[1]
- Objective responses to Rozlytrek were seen in people with CNS metastases at baseline, in both the NTRK and ROS1 populations.[1,2]
- In paediatric patients, Rozlytrek shrank tumours (ORR) in all children and adolescents who had NTRK gene fusions (N=5), with two achieving a complete response (CR). Two patients with primary high-grade tumours in the CNS had objective responses, including one patient with a CR.[1]

F. Hoffmann-La Roche Ltd 4070 Basel Switzerland
Group Communications Roche Group Media Relations
Tel. +41 61 688 88 88 www.roche.com

Across these studies, Rozlytrek was evaluated in several solid tumour types, including sarcoma, non-small cell lung, salivary MASC, secretory and non-secretory breast, thyroid, colorectal, neuroendocrine, pancreatic, ovarian, endometrial carcinoma, cholangiocarcinoma, gastrointestinal cancers and neuroblastoma.[1,2]

Rozlytrek was well tolerated. The most common adverse reactions (≥20 percent) with Rozlytrek were fatigue, constipation, altered sense of taste (dysgeusia), swelling (oedema), dizziness, diarrhoea, nausea, nervous system disorders (dysaesthesia), shortness of breath (dyspnoea), anaemia, increased weight, increased blood creatinine, pain, cognitive disorders, vomiting, cough, and fever (pyrexia).[1,2]

Rozlytrek has been granted Priority Medicines (PRIME) designation by the EMA 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 who have no acceptable standard therapies.[1] A final decision regarding the approval of Rozlytrek by the European Commission is expected in the coming months.

Biomarker testing for NTRK gene fusions and ROS1 in NSCLC across all solid tumours is the only way to identify people who are most eligible for treatment with Rozlytrek. 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 NTRK and ROS1 gene fusions.

About the integrated analysis
The CHMP recommendation is based on an integrated analysis including data from 74 people with locally advanced or metastatic NTRK fusion-positive solid tumours (14 tumour types) and 161 people with ROS1-positive NSCLC from the phase II STARTRK-2, phase I STARTRK-1 and phase I ALKA-372-001 trials.[1,2] It is also based on data from the phase I/II STARTRK-NG study in paediatric patients.[1] The studies enrolled people across 15 countries and more than 150 clinical trial sites. Safety was assessed from an integrated analysis of 504 people across these four trials.[1,2]

About NTRK fusion-positive cancer
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 signalling pathways involved in the proliferation of certain types of cancer.[3] NTRK gene fusions are present in tumours irrespective of site of origin. These fusions have been identified in a broad range of solid tumour types, including sarcoma, non-small cell lung, salivary MASC, secretory and non-secretory breast, thyroid, colorectal, neuroendocrine, pancreatic, ovarian, endometrial carcinoma, cholangiocarcinoma, gastrointestinal cancers and neuroblastoma.[2]

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.[4]

ROS1 gene fusions account for 1-2% of non-small-cell lung cancer (NSCLC).[4] Lung cancer is the leading cause of cancer-related death across the world.[5] 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.[5] NSCLC is the most common

type of lung cancer and accounts for up to 85% of all lung cancer diagnoses.[6] 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.[4]

About Rozlytrek
Rozlytrek® (entrectinib) is a tumour-agnostic, once-daily 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] Rozlytrek can block NTRK and ROS1 kinase activity and may result in the death of cancer cells with NTRK or ROS1 gene fusions.[7,8]

Rozlytrek was granted accelerated approval in August 2019 by the US Food and Drug Administration (FDA), following receipt of Breakthrough Therapy designation, for the treatment of adult and paediatric patients 12 years of age and older with solid tumours that have a NTRK gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy, and was approved for the treatment of adults with ROS1-positive, metastatic NSCLC. In June 2019, Rozlytrek was also approved by Japan's Ministry of Health, Labour and Welfare (MHLW) for the treatment of adult and paediatric patients with NTRK fusion-positive, advanced recurrent solid tumours, and was later approved in ROS1 positive NSCLC in February 2020. Rozlytrek has also received approvals by health authorities in Australia, Canada, Hong Kong, Israel and South Korea.[1]

About Roche in lung cancer
Lung cancer is a major area of focus and investment for Roche, and we are committed to developing new approaches, medicines and tests that can help people with this deadly disease. Our goal is to provide an effective treatment option for every person diagnosed with lung cancer. We currently have five approved medicines to treat certain kinds of lung cancer and more than ten medicines being developed to target the most common genetic drivers of lung cancer or to boost the immune system to combat the disease.

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. More than 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 eleventh consecutive year, Roche has been recognised as one of the most sustainable companies 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 2019 employed about 98,000 people worldwide. In 2019, Roche invested CHF 11.7 billion in R&D and posted sales of CHF 61.5 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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Roche Group Media Relations
Phone: +41 61 688 8888 / e-mail: media.relations@roche.com
- Nicolas Dunant (Head)
- Patrick Barth
- Daniel Grotzky
- Karsten Kleine
- Nathalie Meetz
- Barbara von Schnurbein