# *Media Release*

## Pivotal phase III CLL14 results for Venclexta/Venclyxto in combination with Gazyva/Gazyvaro for chronic lymphocytic leukaemia presented at ASCO 2019 and published in the *New England Journal of Medicine*

- **Venclexta/Venclyxto plus Gazyva/Gazyvaro showed improvements across multiple efficacy measures compared to Gazyva/Gazyvaro plus chlorambucil, including progression-free survival and deep remissions as determined by minimal residual disease measurement**
- **This 12-month, fixed-duration, chemotherapy-free combination was recently approved for previously untreated chronic lymphocytic leukaemia under the FDA's Real-Time Oncology Review pilot programme**

Basel, 4 June 2019 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced results from the pivotal phase III CLL14 study in previously untreated chronic lymphocytic leukaemia (CLL) showing that Venclexta®/Venclyxto® (venetoclax) plus Gazyva®/Gazyvaro® (obinutuzumab) met its primary endpoint of investigator-assessed progression-free survival (PFS). The 12-month, fixed-duration, chemotherapy-free combination reduced the risk of disease worsening or death by 65% compared to Gazyva/Gazyvaro plus chlorambucil (PFS, as assessed by investigator; HR=0.35; 95% CI 0.23-0.53; p<0.001), when given to people with previously untreated CLL who have co-existing medical conditions. The results were presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting and simultaneously published in the *New England Journal of Medicine (NEJM)*.[1,2]

At two years, one year after stopping treatment, nearly nine out of ten patients (88.2%) in the Venclexta/Venclyxto plus Gazyva/Gazyvaro arm remained progression-free, compared to 64.1% in the Gazyva/Gazyvaro plus chlorambucil arm. Safety for Venclexta/Venclyxto plus Gazyva/Gazyvaro appeared consistent with the known safety profiles of the individual medicines. Common Grade 3-4 adverse events with Venclexta/Venclyxto plus Gazyva/Gazyvaro compared to Gazyva/Gazyvaro plus chlorambucil, respectively, were low white blood cell count (52.8% vs. 48.1%) and infections (17.5% vs. 15.0%).

"The results of our phase III CLL14 trial, reported today at ASCO and in the *New England Journal of Medicine*, represent a major advance in improving outcomes in chronic lymphocytic leukaemia," said Sandra Horning, MD, Roche's Chief Medical Officer and Head of Global Product Development. "We are pleased this fixed-duration, chemotherapy-free regimen of Venclexta/Venclyxto plus Gazyva/Gazyvaro was approved by the FDA and look forward to providing an important treatment option to even more adults with the most common form of adult leukaemia."

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The treatment benefit demonstrated with the Venclexta/Venclyxto plus Gazyva/Gazyvaro combination compared to Gazyva/Gazyvaro plus chlorambucil was consistent across secondary endpoints, including:

- Overall response (84.7% vs. 71.3%; p<0.001).
- Complete response with at least partial blood count recovery (49.5% vs. 23.1%; p<0.001).
- Minimal residual disease (MRD)-negativity in the bone marrow (56.9% vs. 17.1%; p<0.001) and peripheral blood (75.5% vs. 35.2%; p<0.001) three months after treatment. MRD-negativity means no cancer can be detected using a specific, highly sensitive test, and was defined as less than one CLL cell in 10,000 white blood cells.

These data were presented at the 2019 ASCO Annual Meeting on Tuesday 4 June 2019, at 10.09-10.21 CST (17.09-17.21, CET; abstract #7502), and simultaneously published in the *NEJM*.

The US Food and Drug Administration (FDA) approved the combination on 15 May 2019, under the FDA's Real-Time Oncology Review and Assessment Aid pilot programmes, for the treatment of people with previously untreated CLL or small lymphocytic lymphoma. This is the second regimen of Roche medicines approved under the RTOR pilot programme, which is exploring a more efficient review process to ensure safe and effective treatments are available to patients as early as possible. Additional submissions of the CLL14 data to health authorities around the world are ongoing.

Venclexta/Venclyxto is being developed by AbbVie and Roche. It is jointly commercialised by AbbVie and Genentech, a member of the Roche Group, in the US and commercialised by AbbVie outside of the US.

**About the CLL14 study** [2]

CLL14 (NCT02242942) is a randomised phase III study evaluating the combination of fixed-duration Venclexta/Venclyxto plus Gazyva/Gazyvaro compared to Gazyva/Gazyvaro plus chlorambucil in patients with previously untreated chronic lymphocytic leukaemia (CLL) and co-existing medical conditions. Co-existing medical conditions included reduced kidney function or co-morbidities assessed by a standard scale (Cumulative Illness Rating Scale). 432 patients with previously untreated CLL were randomly assigned to receive either a 12-month duration of Venclexta/Venclyxto alongside six-month duration of Gazyva/Gazyvaro (Arm A) or six-month duration of Gazyva/Gazyvaro alongside 12-month duration of chlorambucil (Arm B). Arm A started with an initial dosing of Gazyva/Gazyvaro followed by a five-week Venclexta/Venclyxto dose ramp-up to help reduce the risk of tumour lysis syndrome. The primary endpoint of the study is investigator-assessed progression-free survival (PFS). Secondary endpoints include PFS assessed by independent review committee (IRC), minimal residual disease (MRD) status, overall response rate (ORR), complete response (with or without complete blood count recovery), overall survival, duration of response, event-free survival, time to next CLL treatment, and safety. The CLL14 study is being conducted in cooperation with the German CLL Study Group, headed by Michael Hallek, MD, University of Cologne.

After a median follow-up of 28 months, results showed:

- Patients who received Venclexta/Venclyxto plus Gazyva/Gazyvaro lived significantly longer without their disease worsening (PFS, as assessed by investigator) compared to those who received Gazyva/Gazyvaro plus chlorambucil (HR 0.35; 95% CI 0.23-0.53; p<0.001).
    - At two years, 88.2% of patients in the Venclexta/Venclyxto plus Gazyva/Gazyvaro arm had not experienced disease progression, compared to 64.1% with Gazyva/Gazyvaro plus chlorambucil.
    - Median PFS reported by investigators was not yet reached in either arm. IRC assessment of PFS was consistent (HR 0.33; 95% CI, 0.22- 0.51; p<0.001).
- Clinical benefit observed for Venclexta/Venclyxto plus Gazyva/Gazyvaro compared to Gazyva/Gazyvaro plus chlorambucil was consistent across secondary endpoints, including ORR (84.7% vs. 71.3%; p<0.001) and CR including incomplete marrow recovery (49.5% vs. 23.1%; p<0.001).
- In addition, higher rates of MRD-negativity in the bone marrow (56.9% vs. 17.1%; p<0.001) and peripheral blood (75.5% vs. 35.2%; p<0.001) were observed three months after treatment with Venclexta/Venclyxto plus Gazyva/Gazyvaro compared to Gazyva/Gazyvaro plus chlorambucil. MRD-negativity was defined as less than one CLL cell in 10,000 leukocytes.
- Safety for Venclexta/Venclyxto plus Gazyva/Gazyvaro appeared consistent with the known safety profile of the individual medicines, and no new safety signals were identified with the combination. Common Grade 3-4 adverse events with Venclexta/Venclyxto plus Gazyva/Gazyvaro compared to Gazyva/Gazyvaro plus chlorambucil, respectively, were low white blood cell count (52.8% vs. 48.1%) and infections (17.5% vs. 15.0%).

**About Venclexta/Venclyxto (venetoclax)**
Venclexta/Venclyxto is a first-in-class targeted medicine designed to selectively bind and inhibit the B-cell lymphoma-2 (BCL-2) protein. In some blood cancers and other tumours, BCL-2 builds up and prevents cancer cells from dying or self-destructing, a process called apoptosis. Venclexta/Venclyxto blocks the BCL-2 protein and works to restore the process of apoptosis.

Venclexta/Venclyxto is being developed by AbbVie and Roche. It is jointly commercialised by AbbVie and Genentech, a member of the Roche Group, in the US and by AbbVie outside of the US. Together, the companies are committed to research with Venclexta/Venclyxto, which is currently being studied in clinical trials across several types of blood and other cancers.

In the US, Venclexta has been granted five Breakthrough Therapy Designations by the Food and Drug Administration (FDA): in combination with Rituxan for people with relapsed or refractory chronic lymphocytic leukaemia (CLL); as a monotherapy for people with relapsed or refractory CLL with 17p deletion; in combination with hypomethylating agents (azacitidine or decitabine) for people with untreated acute myeloid leukaemia (AML) ineligible for intensive chemotherapy; in combination with low-dose cytarabine (LDAC) for people with untreated AML ineligible for intensive chemotherapy, and in combination with Gazyva in people with previously untreated CLL and co-existing medical conditions.

Venclexta/Venclyxto is approved in more than 50 countries. Roche and AbbVie are currently working with regulatory agencies around the world to bring this medicine to additional eligible patients in need.

**About Gazyva/Gazyvaro (obinutuzumab)**
Gazyva/Gazyvaro is an engineered monoclonal antibody designed to attach to CD20, a protein expressed on certain B-cells, but not on stem cells or plasma cells. Gazyva/Gazyvaro is designed to attack and destroy targeted B-cells both directly and together with the body's immune system. Gazyva is marketed as Gazyvaro in the EU and Switzerland.

Gazyva/Gazyvaro is currently approved in more than 90 countries in combination with chlorambucil for people with previously untreated chronic lymphocytic leukaemia, in more than 80 countries in combination with bendamustine for people with certain types of previously treated follicular lymphoma and in more than 70 countries in combination with chemotherapy for previously untreated follicular lymphoma.

Additional combination studies investigating Gazyva/Gazyvaro with other approved or investigational medicines, including cancer immunotherapies and small molecule inhibitors, are underway across a range of blood cancers.

**About the German CLL Study Group (GCLLSG)**
Founded in 1996 and headed by Michael Hallek, MD, the GCLLSG has been running various phase III, phase II and phase I trials in chronic lymphocytic leukaemia (CLL) with the goal to provide optimal treatment to patients suffering from this disease. Among those were landmark trials like the CLL8 and the CLL11 trials, which led to the current standard of care in CLL. For many years, GCLLSG has been aiming to improve not just the treatment of younger and physically fit patients, but also that of elderly and less fit patients. These patients are generally underrepresented in clinical trials although they constitute the majority of CLL patients treated by doctors in daily practice. The GCLLSG is an independent non-profit research organisation supported by the German Cancer Aid (Deutsche Krebshilfe). www.dcllsg.de

**About Roche in haematology**
Roche has been developing medicines for people with malignant and non-malignant blood diseases for over 20 years; our experience and knowledge in this therapeutic area runs deep. Today, we are investing more than ever in our effort to bring innovative treatment options to patients across a wide range of haematologic diseases. Our approved medicines include MabThera®/Rituxan® (rituximab), Gazyva®/Gazyvaro® (obinutuzumab), Venclexta®/Venclyxto® (venetoclax) in collaboration with AbbVie, and Hemlibra® (emicizumab). Our pipeline of investigational haematology medicines includes polatuzumab vedotin, an anti-CD79b antibody drug conjugate; idasanutlin, a small molecule, which inhibits the interaction of MDM2 with p53; T-cell engaging bispecific antibodies targeting both CD20 and CD3, and Tecentriq® (atezolizumab), a monoclonal antibody designed to bind with PD-L1. Our scientific expertise, combined with the breadth of our portfolio and pipeline, also provides a unique opportunity to develop combination regimens that aim to improve the lives of patients even further.

**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**
[1] Fischer K, et al. Fixed-duration venetoclax plus obinutuzumab (VenG) improves progression-free survival (PFS), and rates and duration of minimal residual disease negativity (MRD–) in previously untreated patients (pts) with chronic lymphocytic leukemia (CLL) and comorbidities. Presented at: ASCO Annual Meeting; 2019 May 31-Jun 4; Chicago, IL, USA. Abstract #7502.
[2] Fischer K, et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. N Engl J Med. 2019; DOI: 10.1056/NEJMoa1815281

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