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Roche reports positive studies of MabThera given by subcutaneous injection Pivotal study data presented at ASH shows that subcutaneous administration enables the delivery of MabThera over approximately 5 minutes without compromising MabThera's proven efficacy and safety

Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced results from two studies which showed that a fixed dose of MabThera (rituximab) can be administered subcutaneously (SC), potentially allowing patients to spend less time in infusion centers receiving their MabThera treatment. Specifically, the studies showed that SC injection resulted in non-inferior MabThera concentrations in the blood (pharmacokinetics; PK) compared with standard intravenous (IV) infusion. Overall, SC and IV adverse event (AE) profiles were similar and administration related reactions (ARR) were mostly of mild to moderate intensity. The results were presented today at the 54th annual meeting of the American Society of Hematology (ASH) and formed the basis of the line-extension marketing application which was submitted to the European Medicines Agency (EMA) on December 4th 2012.

“MabThera SC has the potential to offer patients an effective and more convenient delivery option for MabThera, which has revolutionized the treatment of B-cell malignancies,” said Hal Barron, Chief Medical Officer and Head, Global Product Development. “As a leader in innovative treatments for cancer, Roche is committed to a broad research program of investigational medicines and innovative ways to administer them.”

Administering MabThera SC shortens the treatment time significantly, enabling administration over approximately 5 minutes compared with 2.5 hours during IV infusion. The ready-to-use SC formulation may also significantly reduce pharmacy time and the impact on hospital resources as medicine preparation time and hospital staff time per administration are significantly reduced.

A non-inferiority endpoint was chosen to ensure that patients are not under-dosed as compared to the established IV dose and treatment intervals, and the study met its primary endpoint by confirming that the minimum drug concentration during a given dosing interval (C_{trough}) was non-inferior for MabThera SC vs. IV administration (134.6 vs. 83.1 $\mu\text{g/mL}$ respectively – ratio 1.62). Furthermore, an exploratory efficacy

analysis (response rates) demonstrated that the switch from IV to SC administration did not compromise MabThera's proven anti-lymphoma efficacy.

Additionally, the SparkThera study (phase Ib) also met its primary endpoint of demonstrating non-inferior C_{trough} values of MabThera SC relative to IV when both formulations were given in the follicular lymphoma (FL) maintenance setting. Specifically, the minimum MabThera concentration ratio for SC vs. IV was 1.24 when MabThera was given once every two months and 1.12 when MabThera was given once every three months.

About the SABRINA study (BO22334)

SABRINA is a two-stage international Phase III trial designed to investigate the pharmacokinetics, efficacy and safety of SC versus IV administration of MabThera in FL patients receiving induction and maintenance therapy. In the first stage (dose-confirmation) with pharmacokinetics (C_{trough}) as primary endpoint, treatment-naïve patients with FL, a common type of NHL, were randomized to receive 375 mg/m² MabThera administered intravenously or a fixed dose of 1,400 mg of MabThera via subcutaneous delivery, both given in combination with either CHOP or CVP chemotherapy. Patients who achieved a complete or partial response after 8 treatment cycles continued MabThera maintenance therapy as per their initial randomization with either SC or IV administration. Exploratory efficacy analysis from SABRINA was also performed to demonstrate that a switch from IV to SC administration can be achieved without compromising on MabThera's anti-lymphoma efficacy: Similar overall response rates (ORR) [84.4% IV and 90.5% SC] and complete response (CR) rates [29.7% IV and 46% SC] support the conclusion of comparable efficacy. In the second stage with efficacy as the primary endpoint, additional patients will be randomized to either SC or IV administration of MabThera.

About the SparkThera study (BP22333)

The international Phase Ib study SPARKTHERA is a two-stage study comparing the SC and IV formulations of MabThera in terms of their pharmacokinetics and safety profiles during maintenance treatment in FL patients. In the first (dose-finding) stage of the trial, the dose was selected and in the second stage the selected MabThera SC dose of 1,400mg was confirmed after randomizing patients to receive either SC or IV administration of MabThera during maintenance treatment.

About the MabThera SC formulation

MabThera subcutaneous uses Enhance™ Technology, developed by Halozyme Therapeutics, Inc., which

enables the injection of large volumes of a medication under the skin (subcutaneous). It temporarily modifies a gel-like substance (hyaluronan) that forms a barrier in the tissues between cells under the skin.

Roche is also developing a subcutaneous formulation of Herceptin® (trastuzumab) using this technology and has submitted a Line Extension Application for Herceptin SC to the European Medicines Agency (EMA) for the treatment of HER2-positive breast cancer.

About MabThera

MabThera (rituximab) is a therapeutic monoclonal antibody that binds to a particular protein – the CD20 antigen – on the surface of normal and malignant B-cells. It then recruits the body's natural defenses to attack and kill the marked B-cells. Stem cells (B-cell progenitors) in bone marrow lack the CD20 antigen, allowing healthy B-cells to regenerate after treatment and return to normal levels within several months.

MabThera (Rituxan in the United States), discovered by Biogen Idec, first received FDA approval for the treatment of relapsed indolent non-Hodgkin lymphoma in 1997 and was the first targeted cancer medicine approved by the U.S. Food and Drug Administration (FDA). MabThera was approved in the EU in June 1998. For more than 15 years, the efficacy and safety of MabThera has been documented in more than 300 Phase II/III clinical studies. MabThera has been approved for the treatment of several blood cancers, specifically, certain types of non-Hodgkin lymphoma and for chronic lymphocytic leukemia. It continues to be studied in other types of blood cancers and disease areas where CD20-positive cells are believed to play a role. To date, over 3 million patient exposures with MabThera have been recorded worldwide, 2.7 million of which have been in hematological malignancies.

MabThera is known as Rituxan in the United States, Japan and Canada. Genentech, a member of the Roche family, and Biogen Idec collaborate on Rituxan in the United States, and Roche markets MabThera in the rest of the world, except Japan, where MabThera is co-marketed by Chugai and Zenyaku Kogyo Co. Ltd.

About Roche

Headquartered in Basel, Switzerland, Roche is a leader in research-focused healthcare with combined strengths in pharmaceuticals and diagnostics. Roche is the world's largest biotech company with truly differentiated medicines in oncology, virology, inflammation, metabolism and CNS. Roche is also the world leader in in-vitro diagnostics, tissue-based cancer diagnostics and a pioneer in diabetes management. Roche's personalised healthcare strategy aims at providing medicines and diagnostic tools that enable tangible

improvements in the health, quality of life and survival of patients. In 2011, Roche had over 80,000 employees worldwide and invested over 8 billion Swiss francs in R&D. The Group posted sales of 42.2 billion Swiss francs. Genentech, United States, is a wholly owned member of the Roche Group. Roche has a majority stake in Chugai Pharmaceutical, Japan. For more information: www.roche.com.

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