Novartis breakthrough therapy LEE011 plus letrozole demonstrates superior progression-free survival as first-line treatment for HR+/HER2- advanced breast cancer compared to a standard of care

- LEE011 (ribociclib) plus letrozole reduced the risk of progression or death by 44% over letrozole alone, significantly extending progression-free survival (PFS) across all patient subgroups

- Results showed that the combination significantly improved tumor shrinkage, as more than half of women with measurable disease saw their tumor size shrink by at least 30%1

- Data presented today as late-breaker during the ESMO 2016 Presidential Symposium and published simultaneously in The New England Journal of Medicine to be the basis of worldwide regulatory filings

Basel, October 8, 2016 – Results from the pivotal Phase III MONALEESA-2 study show LEE011 (ribociclib) plus letrozole significantly extended progression-free survival (PFS) compared to a standard of care, letrozole, as a first-line treatment in postmenopausal women with hormone receptor positive, human epidermal growth factor receptor-2 negative (HR+/HER2-) advanced or metastatic breast cancer (median PFS, 95% CI (19.3 months - not reached) vs. 14.7 months (13.0 - 16.5 months); HR=0.556; p=0.00000329)1. Novartis announced today that the data will be featured in the official press briefing at the European Society for Medical Oncology (ESMO) 2016 Congress and presented as a late-breaker during the Presidential Symposium at 16:30 CEST (Abstract LBA1_PR). The results will also be published simultaneously online in The New England Journal of Medicine.

The results demonstrate that LEE011 plus letrozole reduced the risk of death or progression by 44% over letrozole alone. The combination significantly improved PFS across all patient subgroups, regardless of disease characteristics or demographics1. More than half of women with measurable disease taking LEE011 plus letrozole saw their tumor size shrink by at least 30% (overall response rate (ORR) in patients with measurable disease = 53% vs 37%, p=0.00028)1.

“The MONALEESA-2 results show the combination of LEE011 plus letrozole represents a significant step forward in the management of HR+ metastatic breast cancer and, if approved, would be a major addition to the treatment options these patients have,” said Gabriel N. Hortobagyi, MD, Professor of Medicine, Department of Breast Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center and MONALEESA-2 Principal Investigator. “Women living with metastatic breast cancer will be on treatment for the rest of their lives, so it is critical to find treatment options that effectively delay progression.”

Most adverse events in the MONALEESA-2 trial were mild to moderate in severity, identified early through routine monitoring, and generally managed through dose interruption and reduction1. The discontinuation rate due to adverse events in the MONALEESA-2 trial was 7.5% for LEE011 plus letrozole and 2.1% for letrozole alone1.

The most common grade 3/4 (most severe) adverse events were as follows for LEE011 plus letrozole compared to letrozole alone: neutropenia (60% vs 1%), leukopenia (21% vs 1%), elevated alanine aminotransferase (9% vs 1%), lymphopenia (7% vs 1%) and elevated aspartate aminotransferase (6% vs 1%)1. The most common all-grade adverse events (≥35% of patients in
either arm, regardless of relationship to study treatment) were as follows for LEE011 plus letrozole compared to letrozole alone: neutropenia (74% vs 5%), nausea (52% vs 29%), infections (50% vs 42%), fatigue (37% vs 30%), and diarrhea (35% vs 22%). Nausea, infections, fatigue, and diarrhea were mostly grade 1 or 2.

“We are excited about these strong results that show LEE011 has the potential to be an effective first-line treatment option that could improve outcomes for women with HR+/HER2- advanced breast cancer,” said Bruno Strigini, CEO, Novartis Oncology. “Following the Breakthrough Therapy designation granted by the FDA in August of this year, we look forward to working closely with health authorities to bring a much needed new treatment option to these patients as quickly as possible.”

The MONALEESA-2 findings validate the use of a selective CDK4/6 inhibitor in combination with hormonal therapy as initial treatment for HR+/HER2- advanced breast cancer. Due to the significant extension of PFS and clinical benefit seen with LEE011, analysis of the primary endpoint (PFS) in MONALEESA-2 was stopped early in May 2016 as recommended by the Independent Data Monitoring Committee. Follow up to measure overall survival is ongoing.

About LEE011 (ribociclib)
LEE011 (ribociclib) is a selective cyclin dependent kinase inhibitor, a new class of drugs that help slow the progression of cancer by inhibiting two proteins called cyclin dependent kinase 4 and 6 (CDK4/6). These proteins, when over-activated in a cell, can enable cancer cells to grow and divide too quickly. Targeting CDK4/6 with enhanced precision may play a role in ensuring cancer cells do not grow uncontrollably.

LEE011 has been studied in non-clinical models and is currently being evaluated in combination with additional endocrine agents as part of the MONALEESA (Mammary OnCology Assessment of LEE011’s Efficacy and SAFety) clinical trial program. LEE011 is not approved for any indication in any market at this time.

LEE011 was developed by the Novartis Institutes for BioMedical Research (NIBR) under a research collaboration with Astex Pharmaceuticals.

About the MONALEESA Clinical Trial Program
Novartis is continuing to assess LEE011 through the robust MONALEESA clinical trial program, which includes MONALEESA-2, MONALEESA-3, and MONALEESA-7. These trials are evaluating LEE011 in multiple endocrine therapy combinations across a broad range of patients, including men and premenopausal women.

MONALEESA-2 is a Phase III randomized, double blind, placebo controlled, multicenter global registration trial to evaluate the safety and efficacy of LEE011 in combination with letrozole compared to letrozole alone in postmenopausal women with HR+/HER2- advanced breast cancer who received no prior therapy for their advanced breast cancer.

The trial randomized 668 patients in a 1:1 ratio stratified by the presence of liver and/or lung metastases at 223 clinical trial sites globally. Patients received LEE011 600 mg/daily (three weeks on and one week off), or placebo, in combination with letrozole 2.5 mg/daily.

The primary endpoint of the trial was PFS. Secondary endpoints included: overall survival, overall response rate, clinical benefit rate, health-related quality of life, safety and tolerability.

MONALEESA-2 is the only Phase III trial of a CDK4/6 inhibitor in the first-line setting to be stopped early due to superior PFS results, as LEE011 plus letrozole met the primary endpoint at the first efficacy analysis.

The MONALEESA-3 trial is evaluating LEE011 in combination with fulvestrant compared to fulvestrant alone in men and post-menopausal women with HR+/HER2- advanced breast cancer who have received no or a maximum of one prior endocrine therapy.

The MONALEESA-7 trial is investigating LEE011 in combination with endocrine therapy and goserelin compared to endocrine therapy and goserelin alone in pre-menopausal women with HR+/HER2- advanced breast cancer who have not previously received endocrine therapy. Both Phase III trials, MONALEESA-3 and MONALEESA-7 are fully enrolled.
About Advanced Breast Cancer
Up to one-third of patients with early-stage breast cancer will subsequently develop metastatic disease. Metastatic breast cancer is the most serious form of the disease and occurs when the cancer has spread to other parts of the body, such as the brain, bones or liver. Advanced breast cancer comprises metastatic breast cancer (stage 4) and locally advanced breast cancer (stage 3). Survival rates for women living with advanced breast cancer are lower than those for women with earlier stage disease. The 5-year relative survival rate for stage 3 breast cancer is approximately 72%, while metastatic (stage 4) breast cancer has a 5-year relative survival rate of approximately 22%.

About Novartis in advanced breast cancer
For more than 25 years, Novartis has been at the forefront of driving scientific advancements for breast cancer patients and improving clinical practice in collaboration with the global community. With one of the most diverse breast cancer pipelines and the largest number of breast cancer compounds in development, Novartis leads the industry in discovery of new therapies and combinations, especially in HR+ advanced breast cancer, the most common form of the disease.

Disclaimer
The foregoing release contains forward-looking statements that can be identified by words such as "Breakthrough Therapy designation," "continuing," "potential," "will," "upcoming," "commitment," "look forward to," "Fast Track program," "evaluating," "investigating," "pipelines," or similar terms, or by express or implied discussions regarding potential marketing approvals for LEE011, or regarding potential future revenues from LEE011. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that LEE011 will be submitted or approved for sale in any market, or at any particular time. Nor can there be any guarantee that LEE011 will be commercially successful in the future. In particular, management’s expectations regarding LEE011 could be affected by, among other things, the uncertainties inherent in research and development, including unexpected clinical trial results and additional analysis of existing clinical data; unexpected regulatory actions or delays or government regulation generally; the company’s ability to obtain or maintain proprietary intellectual property protection; general economic and industry conditions; competition in general; global trends toward health care cost containment, including ongoing pricing pressures; unexpected manufacturing, safety or quality issues, and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis
Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, eye care and cost-saving generic pharmaceuticals. Novartis is the only global company with leading positions in these areas. In 2015, the Group achieved net sales of USD 49.4 billion, while R&D throughout the Group amounted to approximately USD 8.9 billion (USD 8.7 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 118,000 full-time-equivalent associates. Novartis products are available in more than 180 countries around the world. For more information, please visit http://www.novartis.com.

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References
1. Hortobagyi G, Stemmer S, Burris H, et al. First-line ribociclib plus letrozole for postmenopausal women with HR+, HER2-, advanced breast cancer: First results from the Phase III MONALEESA-2 study. Presented at the European Society for Medical Oncology (ESMO) Congress, October 8, 2016, Copenhagen, Denmark (abstract # LBA1_PR)
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