Novartis International AG
Novartis Global Communications
CH-4002 Basel
Switzerland

https://www.novartis.com
https://twitter.com/novartisnews

MEDIA & INVESTOR RELEASE

FDA approves Novartis Kisqali® to reduce risk of recurrence in people with HR+/HER2- early breast cancer

Ad hoc announcement pursuant to Art. 53 LR

- *Broad indication in HR+/HER2- stage II and III early breast cancer (EBC) at high risk of recurrence approximately doubles population eligible for CDK4/6 inhibitor adjuvant therapy*[1,2]
- *Kisqali® (ribociclib) significantly reduced the risk of recurrence by 25% vs. endocrine therapy (ET) alone; consistent benefit and a well-tolerated safety profile seen across all subgroups in pivotal Phase III NATALEE trial, including patients with node-negative disease*[3-6]
- *Late-breaking NATALEE data recently presented at ESMO provides additional confidence, with deepening of invasive disease-free survival benefit after completion of the three-year treatment period across all patient subgroups*[7]
- *People with stage II or III HR+/HER2- EBC face significant risk of recurrence – often as incurable metastatic disease – despite adjuvant ET and regardless of nodal involvement*[8,9]
- *Already a proven treatment in HR+/HER2- metastatic breast cancer*[1,10-20]*, Kisqali is under regulatory review worldwide, including in the EU, for the EBC indication*

Basel, September 17, 2024 – Novartis today announced that the US Food and Drug Administration (FDA) has approved Kisqali® (ribociclib) in combination with an aromatase inhibitor (AI) for the adjuvant treatment of people with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) stage II and III early breast cancer (EBC) at high risk of recurrence, including those with node-negative (N0) disease[1].

The approval is based on results from the pivotal Phase III NATALEE trial, which showed a significant and clinically meaningful 25.1% (HR=0.749; 95% CI: 0.628, 0.892; *P*=0.0006) reduction in risk of disease recurrence in a broad population of patients with HR+/HER2- stage II and III EBC treated with adjuvant Kisqali plus endocrine therapy (ET) compared to ET alone, including those with high-risk N0 disease[3-6]. The invasive disease-free survival (iDFS) benefit was consistently observed across all patient subgroups[3-6].

“The FDA approval of Kisqali for this early breast cancer population, including those with N0 disease, is a pivotal moment in improving our approach to care,” said Dennis J. Slamon, M.D., Director of Clinical/Translational Research, UCLA Jonsson Comprehensive Cancer Center and Chairman of the Board of Translational Research In Oncology (TRIO) and NATALEE trial

lead investigator. “Today’s approval allows us to offer treatment with a CDK4/6 inhibitor to a significantly broader group of people as a powerful tool that, combined with endocrine therapy, can help further minimize their risk of cancer returning.”

In EBC, Kisqali is taken with or without food as a once-daily oral dose of 400 mg (two 200 mg tablets) for three weeks, followed by one week off treatment, in combination with four weeks of any AI[1]. Patients should take Kisqali for three years. The NATALEE trial showed the safety profile of Kisqali at the 400 mg dose was well tolerated, with discontinuations mainly driven by asymptomatic laboratory findings[3]. Adverse events (AEs) of special interest in the Kisqali + ET arm of the NATALEE trial include (all Grades, and Grades 3/4, respectively): neutropenia (62.5%, 44.3%), liver-related AEs (26.4%, 8.6%), QT interval prolongation (5.3%, 1.0%), and interstitial lung disease/pneumonitis (1.5%, 0.0%)[4].

An updated analysis from the NATALEE trial recently presented at the European Society for Medical Oncology (ESMO) Congress 2024 reinforces the data analyzed by the FDA. Results showed a deepening benefit beyond the three-year treatment period and reduced the risk of recurrence by 28.5% (HR=0.715; CI 95% 0.609–0.840; *P*<0.0001), compared to ET alone, in patients with stage II and III HR+/HER2- EBC[7]. Novartis will continue evaluating NATALEE patients for longer-term outcomes, including overall survival.

Raising the bar for EBC survivors
Approximately 90% of breast cancer cases in the US are diagnosed early (stages I-III) and treated promptly with curative intent – sometimes with adjuvant ET[21,22]. In spite of this, people with stage II and III HR+/HER2- EBC remain at risk of cancer coming back – in most cases, as incurable metastatic disease[8,9]. Recurrence remains a lifelong concern, though most tumors return within the first years, even in cases with no lymph node involvement[8,23]. Despite ET, 10% of people with high-risk N0 disease may face recurrence within the first three years after diagnosis[24].

"With this approval, we are redefining treatment options for a broader population of people impacted by breast cancer and facing the persistent risk of recurrence,” said Victor Bultó, President, US, Novartis. “We continue to transform cancer care with Kisqali, building on its established profile in the metastatic setting and now helping a wide range of people as they strive to stay cancer-free following an early-stage diagnosis.”

"Breast cancer treatment can take a toll on your physical and mental health, and you may worry about the risk of your cancer coming back. This risk is different for everyone, depending on many factors, but should not be underestimated," said Valarie Worthy, Co-Founder & Vice President of Community Outreach and Engagement, Touch, The Black Breast Cancer Alliance. "The FDA approval of Kisqali for more people with breast cancer is welcome news and empowers people diagnosed with early breast cancer with a new option to help manage and control their risk of cancer coming back.”

Novartis prioritizes patient access by offering the Novartis Patient Support program. This resource assists eligible patients in navigating treatment initiation, providing educational materials, clarifying insurance coverage, and identifying potential financial assistance options. For additional information, patients and healthcare professionals can call 1-800-282-7630.

About NATALEE
NATALEE is a global Phase III multi-center, randomized, open-label trial to evaluate the efficacy and safety of Kisqali® (ribociclib) with ET as an investigational adjuvant treatment versus ET alone in patients with stage II and III HR+/HER2- EBC, being conducted in collaboration with TRIO[25]. The adjuvant ET in both treatment arms was a non-steroidal AI (NSAI; anastrozole or letrozole) and goserelin if applicable[25]. The primary endpoint of NATALEE is iDFS as defined by the Standardized Definitions for Efficacy End Points (STEEP) criteria[25]. A total of 5,101 adult patients with HR+/HER2- EBC across 20 countries were randomized in the trial[25].

About Kisqali® (ribociclib)
Kisqali® (ribociclib) is a selective cyclin-dependent kinase inhibitor, a 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, can enable cancer cells to grow and divide too quickly. Targeting CDK4/6 with enhanced precision may play a role in ensuring that cancer cells do not continue to replicate uncontrollably.

Beyond today's FDA approval of Kisqali for EBC patients in the US, regulatory reviews for Kisqali as an EBC treatment are ongoing worldwide, including in the EU and China.

Kisqali has been approved as a treatment for metastatic breast cancer (MBC) patients in 99 countries worldwide, including by the US FDA and the European Commission[1,26]. In the US, Kisqali is indicated for the treatment of adults with HR+/HER2- advanced or MBC in combination with an AI as initial ET or fulvestrant as initial ET or following disease progression on ET in post-menopausal women or in men[1]. In the EU, Kisqali is approved for the treatment of women with HR+/HER2- advanced or MBC in combination with either an AI or fulvestrant as initial ET or following disease progression. In pre- or peri-menopausal women, the ET should be combined with a luteinizing hormone-releasing hormone agonist[26].

In MBC, Kisqali has consistently demonstrated statistically significant overall survival benefit across three Phase III trials[10-20]. The NCCN Guidelines® for breast cancer recommend ribociclib (Kisqali) as the only Category 1 preferred CDK4/6 inhibitor for first-line treatment of people living with HR+/HER2- when combined with an AI, making Kisqali the preferred first-line treatment of choice for US prescribers in HR+/HER2- MBC[27]. Additionally, Kisqali has the highest rating of any CDK4/6 inhibitor on the ESMO Magnitude of Clinical Benefit Scale, achieving a score of five out of five for first-line pre-menopausal patients with HR+/HER2- advanced breast cancer[28]. Further, Kisqali in combination with either letrozole or fulvestrant has uniquely, among other CDK4/6 inhibitors, received a score of four out of five for post-menopausal patients with HR+/HER2- advanced breast cancer treated in the first line[29].

Kisqali was developed by Novartis under a research collaboration with Astex Pharmaceuticals.

Please see full Prescribing Information for Kisqali, available at www.Kisqali.com

About Novartis in Breast Cancer
For more than 35 years, Novartis has been at the forefront of driving scientific advancements for people touched by breast cancer and improving clinical practice in collaboration with the global community. With one of the most comprehensive breast cancer portfolios and pipeline, Novartis leads the industry in discovery of new therapies and combinations in HR+/HER2- breast cancer, the most common form of the disease.

Disclaimer
This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as "potential," "can," "will," "plan," "may," "could," "would," "expect," "anticipate," "look forward," "believe," "committed," "investigational," "pipeline," "launch," "to reduce," "remains," "continue," "transform," "evaluate," "likelihood," "ensuring," "updates," "should," or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for Kisqali in combination with an aromatase inhibitor (AI), or regarding potential future revenues from such product. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations 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 Kisqali in combination with an AI will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that Kisqali in combination with an AI will be commercially successful in the future. In particular, our expectations regarding Kisqali in combination with an AI could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions

or delays or government regulation generally; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political, economic and business conditions, including the effects of and efforts to mitigate pandemic diseases; safety, quality, data integrity or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, 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 is an innovative medicines company. Every day, we work to reimagine medicine to improve and extend people's lives so that patients, healthcare professionals and societies are empowered in the face of serious disease. Our medicines reach more than 250 million people worldwide.

Reimagine medicine with us: Visit us at **https://www.novartis.com** and connect with us on **LinkedIn**, **Facebook**, **X/Twitter** and **Instagram**.

References

1. Kisqali (ribociclib) Prescribing information. East Hanover, New Jersey, USA: Novartis Pharmaceuticals Corporation; September 2024.
2. Tarantino P, Rugo HS, Curigliano G, et al. Characteristics of real-world NATALEE and monarchE eligible populations: A US electronic health records database analysis. Poster presented at the European Society for Medical Oncology Congress; September 13-17, 2024; Barcelona, Spain.
3. Slamon D, Stroyakovskiy D, Yardley D, et al. Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2− early breast cancer: primary results from the Phase III NATALEE trial. Presented at the American Society of Clinical Oncology Annual Meeting; June 2, 2023; Chicago, USA.
4. Hortobagyi G, Stroyakovskiy D, Yardley DA, et al. Ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) as adjuvant treatment in patients with HR+/HER2- early breast cancer: final invasive disease-free survival (iDFS) analysis from the NATALEE trial. Presented at San Antonio Breast Cancer Symposium (SABCS); December 8, 2023; San Antonio, USA.
5. Slamon D et al. Ribociclib plus Endocrine Therapy in Early Breast Cancer. *N Engl J Med*. 2024;390:1080-1091. doi: 10.1056/NEJMoa2305488
6. Yardley D, Untch M, et al. Baseline (BL) characteristics and efficacy endpoints for patients (pts) with node-negative (N0) HR+/HER2− early breast cancer (EBC) in NATALEE. Presented at the American Society of Clinical Oncology Annual Meeting; May 31, 2024; Chicago, USA.
7. Fasching PA. Adjuvant Ribociclib (RIB) Plus Nonsteroidal Aromatase Inhibitor (NSAI) in Patients (Pts) With HR+/HER2− Early Breast Cancer (EBC): 4-Year Outcomes From the NATALEE Trial. LBA13. Proffered Paper presented at the European Society for Medical Oncology Congress; September 16, 2024; Barcelona, Spain.
8. Pan H et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. *N Engl J Med*. 2017;377 (suppl 19):1836 846. doi: 10.1056/NEJMoa1701830
9. Wangchinda P, Ithimakin S. Factors that predict recurrence later than 5 years after initial treatment in operable breast cancer. *World J Surg Oncol*. 2016;14(1):223. doi: 10.1186/s12957-016-0988-0
10. Yardley DA, Yap YS, et al. Pooled exploratory analysis of survival in patients (pts) with HR+/HER2- advanced breast cancer (ABC) and visceral metastases (mets) treated with ribociclib (RIB) + endocrine therapy (ET) in the MONALEESA (ML) trials. Poster presented at the European Society of Medical Oncology Congress; September 9-13, 2022; Paris, France.
11. Neven P, Fasching PA, et al. Updated overall survival (OS) results from the first-line (1L) population in the Phase III MONALEESA-3 trial of postmenopausal patients with HR+/HER2- advanced breast cancer (ABC) treated with ribociclib (RIB) + fulvestrant (FUL). Mini oral presented at the European Society for Medical Oncology Breast Cancer Congress; May 4, 2022; Paris, France.
12. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer. *N Engl J Med*. 2022;386(10):942-950. doi:10.1056/NEJMoa2114663
13. Hortobagyi GN, et al. Overall survival (OS) results from the phase III MONALEESA (ML)-2 trial of postmenopausal patients with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib. Proffered paper presented at the European Society of Medical Oncology Congress; September 16-21, 2021; Lugano, Switzerland.
14. Im S-A, Lu Y-S, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med*. 2019;381(4):307-316. doi:10.1056/nejmoa1903765
15. Slamon DJ, Neven P, Chia S, et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. *N Engl J Med*. 2020;382(6):514-524. doi:10.1056/NEJMoa1911149
16. Slamon DJ, Neven P, Chia S, et al. Overall survival (OS) results of the Phase III MONALEESA-3 trial of postmenopausal patients (pts) with hormone receptor–positive (HR+), human epidermal growth factor 2–negative (HER2−) advanced breast cancer (ABC) treated with fulvestrant (FUL) ± ribociclib (RIB). Presented at the European Society of Medical Oncology Congress; September 29, 2019; Barcelona, Spain.

17. Slamon DJ, Neven P, Chia S, et al. Updated overall survival (OS) results from the Phase III MONALEESA-3 trial of postmenopausal patients (pts) with HR+/HER2− advanced breast cancer (ABC) treated with fulvestrant (FUL) ± ribociclib (RIB. Presented at the American Society of Clinical Oncology Annual Meeting; June 5, 2021; Chicago, USA.
18. Tripathy D, Im S-A, Colleoni M, et al. Updated overall survival (OS) results from the phase III MONALEESA-7 trial of pre- or perimenopausal patients with HR+/HER2− advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib. Presented at the San Antonio Breast Cancer Symposium; December 9, 2020; San Antonio, USA.
19. Yardley D, Nusch A, Yap YS, et al. Overall survival (OS) in patients (pts) with advanced breast cancer (ABC) with visceral metastases (mets), including those with liver mets, treated with ribociclib (RIB) plus endocrine therapy (ET) in the MONALEESA (ML) -3 and -7 trials. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; June 2020; Chicago, USA.
20. O'Shaughnessy J, Stemmer SM, Burris HA, et al. Overall survival subgroup analysis by metastatic site from the Phase III MONALEESA-2 study of first-line ribociclib + letroz21ole in postmenopausal patients with HR+/HER2− advanced breast cancer. Presented at the San Antonio Breast Cancer Symposium; December 7-10, 2021; San Antonio, USA.
21. Iqbal J, Ginsburg O, Rochon PA, Sun P, Narod SA. Differences in breast cancer stage at diagnosis and cancer-specific survival by race and ethnicity in the United States [published correction appears in *JAMA*. 2015 Jun 9;313(22):2287]. *JAMA*. 2015;313(2):165-173. doi:10.1001/jama.2014.17322
22. American Cancer Society. Cancer Facts and Figures. Published 2024. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2024/2024-cancer-facts-and-figures-acs.pdf. Accessed September 2024.
23. Gomis R, Gawrzak S. Tumor cell dormancy. *Mol Oncol.* 2017;11(1):62-78.
24. Curigliano G, Ciruelos E, et al. Meta analysis of ET control arms in adjuvant trials. Presented at the American Society of Clinical Oncology Annual Meeting; May 31, 2024; Chicago, USA.
25. Clinicaltrials.gov. NCT03701334. A Trial to Evaluate Efficacy and Safety of Ribociclib With Endocrine Therapy as Adjuvant Treatment in Patients With HR+/ HER2- Early Breast Cancer (NATALEE). Accessed September 2024. https://clinicaltrials.gov/study/NCT03701334
26. Kisqali. Summary of product characteristics (SmPC). Novartis Europharm Limited; 2017. Accessed September 2024. https://www.ema.europa.eu/en/documents/product-information/kisqali-epar-product-information_en.pdf.
27. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) - Breast Cancer. NCCN Guidelines. Published March 2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed September 2024.
28. European Society for Medical Oncology – Magnitude of Clinical Benefit Scale Scorecard. Published April 20, 2020. Updated August 21, 2020. Available at: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-158-1/. Accessed September 2024.
29. European Society for Medical Oncology – Magnitude of Clinical Benefit Scale Scorecard. Published March 29, 2022. Available at: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-9-1/. Accessed September 2024.

# # #

Novartis Media Relations
E-mail: media.relations@novartis.com

Central		North America	
Anja von Treskow	+41 79 392 9697	Michael Meo	+1 862 274 5414
Anna Schäfers	+41 79 801 7267		
Switzerland			
Satoshi Sugimoto	+41 79 619 2035		

Novartis Investor Relations
Central investor relations line: +41 61 324 7944
E-mail: investor.relations@novartis.com

Central		North America	
Isabella Zinck	+41 61 324 7188	Sloan Simpson	+1 862 345 4440
Nicole Zinsli-Somm	+41 61 324 3809	Jonathan Graham	+1 201 602 9921
Imke Kappes	+41 61 324 8269	Parag Mahanti	+1 973 876 4912