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MEDIA & INVESTOR RELEASE

Novartis Scemblix® FDA approved in newly diagnosed CML, offering superior efficacy, and favorable safety and tolerability profile

Ad hoc announcement pursuant to Art. 53 LR

- *Scemblix, a new first-line option for adults with CML, is first to show superior efficacy and favorable safety and tolerability profile in a Phase III trial vs. all standard of care (SoC) therapies*[1-3]
- *Patients on Scemblix also had fewer dose reductions and half the rate of adverse reactions leading to treatment discontinuation*[1-3]
- *Nearly 50% of CML patients do not meet efficacy milestones (MMR) with current SoC and almost 25% discontinue or switch therapies within one year of treatments*[4-5]
- *Scemblix now approved for newly diagnosed and previously treated CML, allowing four times the patients access to potential new standard of care*

Basel, October 29, 2024 – Novartis announced today that Scemblix® (asciminib) was granted accelerated approval by the US Food and Drug Administration (FDA) for adult patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase (Ph+ CML-CP).

The accelerated approval is based on major molecular response rate (MMR) at week 48 from the ASC4FIRST Phase III trial that compared once daily Scemblix to all other investigator-selected (IS) standard of care (SoC) tyrosine kinase inhibitors (TKIs) (imatinib, nilotinib, dasatinib, and bosutinib). In the study, Scemblix demonstrated superior MMR rates in both primary endpoints at week 48 vs. IS SoC TKIs and imatinib alone[1-3]. Continued approval for the newly diagnosed indication may be contingent upon verification and description of clinical benefit from confirmatory evidence.

The expanded indication in Ph+ CML-CP increases the population eligible for Scemblix by approximately four times, including newly diagnosed and previously treated adults. Newly diagnosed patients will now have access to a treatment that has shown superior efficacy vs. all standard of care therapies and a favorable safety and tolerability profile.

“Many patients who are newly diagnosed with CML struggle to navigate this chronic condition and may switch or even stop treatment because of side effects that interrupt their daily lives,” said Lee Greenberger, Ph.D., Chief Scientific Officer at The Leukemia & Lymphoma Society. “That’s why approvals of new first-line treatment options are so important. For

patients, finding a medicine that's right for them at the very beginning of treatment may lead to better long-term disease control with fewer side effects."

While TKIs have transformed CML into a chronic disease, efficacy and safety challenges continue to hinder long-term treatment success for many patients. Many newly diagnosed patients do not meet molecular response goals, and many discontinue or change treatment due to intolerance[4-23]. Nearly half of CML patients do not meet efficacy milestones (MMR) and almost one in four patients discontinue or switch treatment within one year[4-5].

"While there are a range of effective TKIs currently available for newly diagnosed patients, clinicians frequently have had to weigh sacrificing either efficacy or tolerability," said Jorge Cortes, M.D., Director, Georgia Cancer Center. "In the first-of-its-kind ASC4FIRST trial, Scemblix achieved impressive results across all three parameters of efficacy, safety and tolerability versus all standard of care TKIs. This Scemblix data has the potential to be practice-changing."

The FDA approval of Scemblix is based on results from the Phase III ASC4FIRST trial in patients newly diagnosed with Ph+ CML-CP. Data showed:

- Nearly 20% more patients treated with Scemblix achieved MMR vs. IS SoC TKIs (imatinib, nilotinib, dasatinib and bosutinib) (68% vs. 49%, < 0.001) and nearly 30% more patients achieved MMR vs. imatinib alone (69% vs. 40%, < 0.001) at week 48[1-2]
- Scemblix is the first CML treatment to show superior efficacy along with a favorable safety and tolerability profile vs. imatinib and second generation TKIs, with fewer treatment-related grade ≥3 ARs (25.5% vs. 33% and 42%), dose reductions (6% vs. 14% and 24%), and half the rate of ARs leading to treatment discontinuation (4.5% vs. 11% and 9.8%)[1-3]
- Patients treated with Scemblix also achieved deeper rates of molecular responses including MR4 compared with IS-TKIs and imatinib alone (41% vs. 22% and 16%) by week 48[1-2]
- In newly diagnosed patients, the safety profile was consistent with previous registration studies with no new safety concerns observed. The most common ARs (≥ 20%) were musculoskeletal pain, rash, fatigue, upper respiratory tract infection, headache, abdominal pain and diarrhea[1-3]

The ASC4FIRST trial remains ongoing, with the next scheduled analysis at week 96 to evaluate the key secondary endpoint (MMR at week 96) and additional secondary endpoints.

The approval was also supported by preliminary data from the Phase II ASC2ESCALATE study, which includes Ph+ CML-CP patients who have been previously treated with one prior TKI with discontinuation due to treatment failure, warning, or intolerance. Data will be shared at a future medical meeting.

"We are proud to help redefine CML treatment once again with Scemblix, as we continue to deliver on our 20+ year commitment to innovation and support in CML," said Victor Bulto, President US, Novartis. "Despite many advances in the field, patients still need treatment options that are highly effective with a favorable tolerability profile to help enable them to achieve meaningful outcomes as they manage chronic conditions. With this approval, we can offer newly diagnosed adult Ph+ CML-CP patients a new treatment option that combines both, with the potential to change the trajectory of many more people living with CML."

About ASC4FIRST Phase III Clinical Trial

ASC4FIRST (NCT04971226) is a Phase III, head-to-head, multi-center, open-label, randomized study of oral Scemblix® 80 mg QD vs. IS first- or second-generation TKIs (imatinib, nilotinib, dasatinib or bosutinib) in 405 adult patients with newly diagnosed Ph+ CML-CP[1,24]. The two primary endpoints of the study are to compare efficacy of asciminib vs. IS SoC TKIs and to compare efficacy vs. that of TKI within the stratum of participants with

imatinib as pre-randomization selected TKI, based on proportion of patients that achieve MMR at week 48[1,24].

The study remains ongoing with key secondary endpoints of proportion of patients that achieve MMR at week 96 and a safety endpoint of discontinuation of study treatment due to an AE (TTDAE) by week 96[1,24]. The study also assesses additional secondary safety and efficacy endpoints, including MMR, MR4, MR4.5, complete hematological response (CHR) and BCR::ABL1 ≤1% at and by all scheduled data collection time points; duration of and time to first MMR, MR4 and MR4.5; time to treatment failure; event-free survival, failure-free survival, progression-free survival and overall survival[1,24].

About Scemblix® (asciminib)
Scemblix® is the first CML treatment that works by Specifically Targeting the ABL Myristoyl Pocket (referred to as a STAMP inhibitor in scientific literature)[25-27]. The current approved CML treatments are TKIs that target the ATP-binding site (ATP-competitive) [27].

Scemblix was granted accelerated approval in the US to treat newly diagnosed adults and is also approved for previously treated adult patients with Ph+ CML-CP. Scemblix received Breakthrough Therapy designation for the treatment of newly diagnosed adult patients and was reviewed under the FDA's Real-Time Oncology Review (RTOR) program[28-30]. It is approved in more than 75 countries, including the EU, to treat those who have previously been treated with two or more TKIs with Ph+ CML-CP[28,29,31]. In some countries, including the US, Scemblix is also approved in patients with Ph+ CML-CP with the T315I mutation[28-30].

Scemblix is being studied across multiple treatment lines for Ph+ CML-CP, both as a monotherapy and in combination[1,24-26,29,32-44].

Patient Access and Support
Novartis, with its 20+ year history in CML, is committed to continuing to address areas of unmet patient need and reducing barriers to patient access and affordability that prevent patients from benefiting from innovation. Novartis Patient Support is available to help guide eligible patients through the various aspects of getting started on treatment including help understanding insurance coverage and identifying potential financial assistance options. Patients or providers can call 866-433-8000 or visit support.scemblix.com to learn more.

About Novartis Commitment to CML
Novartis has a long-standing scientific commitment to patients living with CML. For more than two decades, our bold science has helped transform CML from a life-limiting condition for many patients. Despite these advancements, there's still work to be done. We continue to research ways to target the disease more selectively and to address the challenges of not reaching treatment efficacy goals, experiencing treatment resistance and/or intolerance that many patients face. Our legacy inspires our future innovation – we continue to lead the way in developing novel medicines to address serious unmet needs in CML. Our commitment also goes beyond science. Our 20+ year collaboration with the Max Foundation has provided access to Gleevec (imatinib), Tasigna (nilotinib) and now Scemblix and is delivering tremendous patient impact in low- and middle-income countries, with over 100,000 patients supported to date.

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," "may," "committed," "contingent," "lead," "continue," "ongoing," "to deliver," "allowing," "continuing," "commitment," or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for Scemblix, or regarding potential future revenues from Scemblix. 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 Scemblix 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 Scemblix will be commercially successful in the future. In particular, our expectations regarding Scemblix 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. Scemblix (asciminib) Prescribing information. East Hanover, New Jersey, USA: Novartis Pharmaceuticals Corporation; October 2024.
2. Hochhaus A, Wang J, Dong-Wook K, et al. Asciminib in Newly Diagnosed Chronic Myeloid Leukemia. *N Engl J Med.* 2024. doi:10.1056/NEJMoa2400858
3. CABL001J SCS/RMP. Novartis Pharmaceuticals Corp; 2024.
4. Kota VK, Wei D, Yang D, et al. Treatment Patterns and Modifications of Tyrosine Kinase Inhibitors (TKI) Therapy in Early Lines in Patients with Chronic Myeloid Leukemia in Chronic Phase (CML-CP): Real-World Analysis from a Large Commercial Claims Database in the United States (US). *Blood.* 2023;142:5190.
5. Hochhaus, A., & Ernst, T. 2021. TKI discontinuation in CML: How do we make more patients eligible? How do we increase the chances of a successful treatment-free remission? Hematology Am Soc Hematol Educ Program, 2021(1), 106–112.
6. Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. *Leukemia*. 2016;30(5):1044-1054. doi:10.1038/leu.2016.5
7. Brümmendorf TH, Cortes JE, de Souza CA, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukaemia: results from the 24-month follow-up of the BELA trial. *Br J Haematol*. 2015;168(1):69-81. doi:10.1111/bjh.13108
8. Cortes JE, Gambacorti-Passerini C, Deininger MW, et al. Bosutinib Versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia: Results From the Randomized BFORE Trial. *J Clin Oncol*. 2018;36(3):231-237. doi:10.1200/JCO.2017.74.7162
9. Hehlmann R, Cortes JE, Zyczynski T, et al. Tyrosine kinase inhibitor interruptions, discontinuations and switching in patients with chronic-phase chronic myeloid leukemia in routine clinical practice: SIMPLICITY. *Am J Hematol*. 2019;94(1):46-54. doi:10.1002/ajh.25306
10. Claudiani S, Chughtai F, Khan A. et al. Long-term outcomes after upfront second-generation tyrosine kinase inhibitors for chronic myeloid leukemia: managing intolerance and resistance. *Leukemia.* 2024;38:796 - 802. doi:10.1038/s41375-024-02187-w
11. Kohlbrenner K, Galuschek N, Fabarius A, et al. Therapy in Patients with Chronic Myeloid Leukemia Outside of Clinical Trials: Results of the German CML-Registry (CML-VI). *Blood.* 2022;140(Supplement 1):947 - 949. doi:10.1182/blood-2022-159412
12. Cortes JE, Khoury HJ, Kantarjian HM, et al. Long-term bosutinib for chronic phase chronic myeloid leukemia after failure of imatinib plus dasatinib and/or nilotinib. *Am J Hematol.* 2016;91(12):1206-1214. doi:10.1002/ajh.24536
13. Garg RJ, Kantarjian H, O'Brien S, et al. The use of nilotinib or dasatinib after failure to 2 prior tyrosine kinase inhibitors: long-term follow-up. *Blood.* 2009;114(20):4361-4368. doi:10.1182/blood-2009-05-221531
14. Steegmann JL., Baccarani M, Breccia M, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. *Leukemia.* 2016;30:1648-1671. doi:10.1038/leu.2016.104

15. Hochhaus A, Larson RA, Guilhot F, et al. Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. *N Engl J Med.* 2017;376: 917 - 927. doi:10.1056/NEJMoa1609324
16. Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial. *J Clin Oncol.* 2016;34:2333-2340. doi:10.1200/JCO.2015.64.8899
17. Akard LP, Albitar M, Hill CE, Pinilla-Ibarz, J. The "Hit Hard and Hit Early" Approach to the Treatment of Chronic Myeloid Leukemia: Implications of the Updated National Comprehensive Cancer Network Clinical Practice Guidelines for Routine Practice. *Clin Adv Hematol Oncol.* 2013;11(7):421-432.
18. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. Ponatinib efficacy and safety in Philadelphia chromosome–positive leukemia: final 5-year results of the phase 2 PACE trial. *Blood.* 2018;132(4):393-404. doi:10.1182/blood-2016-09-739086
19. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia.* 2020;34:966-984. doi:10.1038/s41375-020-0776-2
20. Flis S, Chojnacki T. Chronic myelogenous leukemia, a still unsolved problem: pitfalls and new therapeutic possibilities. *Drug Des Devel Ther.* 2019;13:825-843. doi:10.2147/DDDT.S191303
21. Cortes, J., Lang, F. Third-line therapy for chronic myeloid leukemia: current status and future directions. *J Hematol Oncol.* 2021;14:44. doi:10.1186/s13045-021-01055-9
22. Shyam Sunder S., Sharma UC, Pokharel S. Adverse effects of tyrosine kinase inhibitors in cancer therapy: pathophysiology, mechanisms and clinical management. *Sig Transduct Target Ther*. 2023;8:262. doi:10.1038/s41392-023-01469-6
23. Yoshifuji K, Sasaki K. Adverse events and dose modifications of tyrosine kinase inhibitors in chronic myelogenous leukemia. *Front Oncol*. 2022;12. doi:10.3389/fonc.2022.1021662
24. A Study of Oral Asciminib Versus Other TKIs in Adult Patients With Newly Diagnosed Ph+ CML-CP (ASC4FIRST). ClinicalTrials.gov identifier: NCT04971226. Updated March 25, 2024. Accessed March 26, 2024. https://clinicaltrials.gov/study/NCT04971226
25. Rea D, Mauro MJ, Boquimpani C, et al. A Phase 3, Open-Label, Randomized Study of Asciminib, a STAMP Inhibitor, vs Bosutinib in CML After 2 or more prior TKIs. *Blood.* 2021;138(21):2031-2041. doi:10.1182/blood.2020009984
26. Cortes JE, Hughes TP, Mauro MJ, et al. Asciminib, a First-in-Class STAMP Inhibitor, Provides Durable Molecular Response in Patients (pts) with Chronic Myeloid Leukemia (CML) Harboring the T315I Mutation: Primary Efficacy and Safety Results from a Phase 1 Trial. Oral presentation at: ASH Annual Meeting; Dec. 7, 2020.
27. Schoepfer J, Jahnke W, Berellini G, et al. Discovery of Asciminib (ABL001), an Allosteric Inhibitor of the Tyrosine Kinase Activity of BCR-ABL1. *J Med Chem.* 2018;61(18):8120-8135. doi:10.1021/acs.jmedchem.8b01040
28. Scemblix. US FDA Prescribing Information. Novartis Pharmaceuticals; 2021.
29. Novartis data on file.
30. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Chronic Myeloid Leukemia Version 2.2024. December 5, 2023. Accessed April 3, 2024. https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf
31. Scemblix. EMA Summary of Product Characteristics. Novartis Europharm Limited; 2022.
32. Wylie AA, Schoepfer J, Jahnke W, et al. The allosteric inhibitor ABL001 enables dual targeting of BCR–ABL1. *Nature.* 2017;543(7647):733-737. doi:10.1038/nature21702
33. Hughes TP, Mauro MJ, Cortes JE, et al. Asciminib in Chronic Myeloid Leukemia after ABL Kinase Inhibitor Failure. *N Engl J Med.* 2019; 381(24):2315-2326. doi:10.1056/NEJMoa1902328
34. Hughes TP, et al. Expanded Phase 1 Study of ABL001, a Potent, Allosteric Inhibitor of BCR-ABL, Reveals Significant and Durable Responses in Patients with CML-Chronic Phase with Failure of Prior TKI Therapy. Presented at: ASH Annual Meeting & Exposition; Dec. 5, 2016.
35. Ottmann OG, Alimena G, DeAngelo DJ, et al. ABL001, a Potent, Allosteric Inhibitor of BCR-ABL, Exhibits Safety and Promising Single- Agent Activity in a Phase I Study of Patients with CML with Failure of Prior TKI Therapy. *Blood.* 2015;126(23):138. doi:10.1182/blood.V126.23.138.138
36. Mauro MJ, Kim DW, Cortes J, et al. Combination of Asciminib Plus Nilotinib (NIL) or Dasatinib (DAS) in Patients (PTS) with Chronic Myeloid Leukemia (CML): Results from a Phase 1 Study. Presented at: EHA Annual Meeting; June 15, 2019.
37. Cortes JE, Lang F, Kim DW, et al. Combination Therapy Using Asciminib Plus Imatinib (IMA) in Patients (PTS) with Chronic Myeloid Leukemia (CML): Results from a Phase 1 Study. Presented at: EHA Annual Meeting; June 15, 2019.
38. Manley PW, Barys L, Cowan-Jacob SW. The specificity of asciminib, a potential treatment for chronic myeloid leukemia, as a myristate-pocket binding ABL inhibitor and analysis of its interactions with mutant forms of BCR-ABL1 kinase. *Leuk Res.* 2020;98:106458. doi:10.1016/j.leukres.2020.106458
39. Study of Efficacy of CML-CP Patients Treated with ABL001 Versus Bosutinib, Previously Treated With 2 or More TKIs. ClinicalTrials.gov identifier: NCT03106779. Updated February 7, 2024. Accessed April 3, 2024. https://clinicaltrials.gov/ct2/show/NCT03106779
40. Asciminib in Monotherapy for Chronic Myeloid Leukemia in Chronic Phase (CML-CP) With and WithoutT315I Mutation (AIM4CML). ClinicalTrials.gov identifier: NCT04666259. Updated September 7, 2023. Accessed April 3, 2024. https://clinicaltrials.gov/ct2/show/NCT04666259
41. Study of Efficacy And Safety Of Asciminib In Combination With Imatinib In Patients With Chronic Myeloid Leukemia In Chronic Phase (CML-CP). ClinicalTrials.gov identifier: NCT03578367. Updated March 22, 2024. Accessed April 3, 2024. https://clinicaltrials.gov/ct2/show/NCT03578367
42. Study of Efficacy and Safety of CML-CP Patients Treated With Asciminib Versus Best Available Therapy, Previously Treated With 2 or More Tyrosine Kinase Inhibitors. ClinicalTrials.gov identifier: NCT04795427. Updated October 19, 2023. Accessed April 3, 2024. https://clinicaltrials.gov/ct2/show/NCT04795427
43. A Phase I Study of Oral ABL001 in Patients With CML or Ph+ ALL. ClinicalTrials.gov identifier: NCT02081378. Updated March 18, 2024. Accessed April 3, 2024. https://clinicaltrials.gov/ct2/show/NCT02081378

44. Asciminib Treatment Optimization in ≥ 3rd Line CML-CP. ClinicalTrials.gov identifier: NCT04948333. Updated February 28, 2024. Accessed April 3, 2024. https://clinicaltrials.gov/ct2/show/NCT04948333

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