Avillion Announces US Approval of Pfizer's BOSULIF® (bosutinib) for the Treatment of Patients with Newly-Diagnosed Ph+ Chronic Myelogenous Leukemia (CML)

Approval based on the successful BFORE Phase 3 study conducted by Avillion under a collaborative development agreement with Pfizer

London, UK, December 19, 2017 – Avillion LLP, a drug development company focused on the co-development and financing of pharmaceutical candidates from proof-of-concept through to regulatory approval, announces that the U.S. Food and Drug Administration (FDA) today approved a supplemental New Drug Application (sNDA) for Pfizer's BOSULIF® (bosutinib). The approved sNDA expands the indication for BOSULIF to include the treatment of adult patients with newly-diagnosed chronic phase Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML).

The approval was based on positive results from the randomized, multinational BFORE Phase 3 study, which was conducted successfully by Avillion under an exclusive collaborative development agreement with Pfizer. The sNDA was reviewed and approved under the FDA's Priority Review and accelerated approval program based on molecular and cytogenetic response rates demonstrated by BOSULIF. BOSULIF is also indicated in the U.S. for the treatment of adult patients with chronic, accelerated or blast phase Ph+ CML with resistance or intolerance to prior therapy.

Avillion provided funding and undertook the BFORE study to generate the clinical data used to support this application and other potential regulatory filings for marketing authorisation for BOSULIF as first-line treatment for patients with chronic phase Ph+ CML. Avillion is eligible to receive milestone payments from Pfizer based on this approval. Pfizer retains all rights to commercialize BOSULIF globally.

Prof. Tim H. Brümmendorf, Director of the Clinic for Oncology, Haematology and Stem Cell Transplantation at the Euregionales Comprehensive Cancer Center Aachen (ECCA), and European lead investigator on BFORE, added: "Molecular targeted therapy has substantially improved outcomes of patients with CML over that last two decades. Due to its efficacy and distinct tolerability profile, BOSULIF significantly expands our treatment options for newly diagnosed CML patients."

Allison Jeynes-Ellis, MD, Chief Executive Officer of Avillion, said: "We are delighted with the approval today of BOSULIF by the US FDA. It not only adds an important treatment option for newly diagnosed Ph+ CML patients, but also represents a significant validation of our innovative business model and capabilities for the co-development and partnership of late-stage clinical candidates. Our model provides pharma partners with opportunities and capacity to advance additional late-stage clinical projects in parallel to their own development efforts. This achievement is testament to the expertise and hard work of the teams at Avillion and Pfizer, and we look forward to replicating this success in other partnerships."

"Today's approval is a testament to the strength of our partnership with Avillion and to the commitment of both of our companies to work together to improve lives for patients living with CML," added Liz Barrett, Global President, Pfizer Oncology.

Efficacy and safety data support BOSULIF approval

The BOSULIF approval was based on results from BFORE (Bosutinib trial in First line chrOnic myelogenous leukemia tREatment), a randomized multi-center, multinational, open-label Phase 3 study which showed BOSULIF 400 mg was associated with a significantly higher rate of patients achieving major molecular response (MMR) at 12 months (47.2%; 95% CI, 40.9-53.4) compared to the rate achieved in patients treated with imatinib 400mg (36.9%; 95% CI, 30.8-43.0), a current standard of care. Complete cytogenic response (CCyR) rate by 12 months was 77.2% for patients treated with BOSULIF compared to 66.4% for patients treated with imatinib (P<0.008), with time to CCyR shorter for patients treated with BOSULIF (HR 1.38; P$\leqslant$0.001). The adverse events seen in the trial were consistent with the known safety profile for BOSULIF. The most common adverse events in newly diagnosed CML patients treated with BOSULIF (incidence $\geqslant$20%) are diarrhea, nausea, thrombocytopenia, increased alanine aminotransferase (ALT), rash, abdominal pain, and increased aspartate aminotransferase (AST). For more information, please see Important Safety Information for BOSULIF below.

About Chronic Myelogenous Leukemia (CML)

Chronic myelogenous leukemia (CML) is a rare blood cancer, which begins in the bone marrow, but often moves into the blood.[1] Researchers estimate that by 2020, more than 412,000 people worldwide will be diagnosed with leukemia (all types)[2]. CML accounts for 10-15% of all incident leukemia cases.[3] In the U.S., approximately 48,000 people are living with CML.[1] Around 9,000 new CML cases were diagnosed in the U.S. in 2017.[2]

[1]American Cancer Society. What is Chronic Myeloid Leukemia? [Link] Accessed August 2017.
[2]GLOBOCAN Online Analysis/Prediction. [Link] Accessed August 2017.
[3]Hochhaus, A. Educational Session: Managing Chronic Myeloid Leukemia as a Chronic Disease. American Society of Hematology. 2011; 10: 1.

About BOSULIF® (bosutinib)

BOSULIF® (bosutinib) is an oral, once-daily, tyrosine kinase inhibitor (TKI), which inhibits the Bcr-Abl kinase that promotes CML; it is also an inhibitor of Src-family kinases. In the U.S., BOSULIF (bosutinib) is now indicated for the treatment of patients with newly-diagnosed chronic phase Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) and for the treatment of adult patients with chronic, accelerated or blast phase Ph+ CML with resistance or intolerance to prior therapy (first approved in September 2012). A 400mg tablet was also recently approved by the FDA in addition to the previously approved 100mg and 500mg strengths. The recommended dose for newly diagnosed patients is 400 mg orally once daily with food. For patients who are resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy, the recommended dose is 500mg orally once daily with food.

In Europe, BOSULIF was granted conditional marketing authorization in March 2013 for the treatment of adult patients with Ph+ CML previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. The European Medicines Agency (EMA) has also validated for review a Type II Variation application for use of BOSULIF in the same patient population.

About the BFORE Study

BFORE (Bosutinib trial in First line chrOnic myelogenous leukemia tREatment) is a multi-center, open-label Phase 3 study designed to assess the effectiveness and safety of BOSULIF® (bosutinib) as a first-line treatment for patients with chronic phase Ph+ CML. The study enrolled 536 patients at multiple sites in North America, Asia and Europe. Patients were randomized 1:1 to receive BOSULIF

400mg or imatinib, a standard of care, for the duration of the study. The primary outcome was to show superiority of bosutinib over imatinib at 12 months by comparing MMR, or the proportion of patients in each arm whose levels of the Bcr-Abl1 kinase have dropped below 0.1%.

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About Avillion

Avillion LLP is a drug development company with an innovative business model focusing on the clinical co-development and regulatory approval of pharmaceutical products. Avillion offers a compelling opportunity to partner assets from post proof of concept through to regulatory approval globally and to accelerate their development and hence availability to patients. Avillion's objective is to enable its partners to continue to develop the drug candidates in their pipeline whilst maintaining quality data without increasing the burden on their P&L or cash reserves. Avillion can achieve this by incurring 100% of the clinical and regulatory risk, while advancing the development of these assets in return for milestone and royalty payments on the commercialisation of successfully developed products.

To date, Avillion has advanced Pfizer's BOSULIF® (bosutinib) successfully through Phase 3 trials and providing the clinical data to gain US approval to expand its use to include patients with newly diagnosed chronic phase Philadelphia chromosome-positive (Ph+) chronic myeloid leukaemia.

Avillion is also undertaking Phase 2 trials with Merck's anti IL-17 A/F Nanobody® in plaque psoriasis.

Avillion was founded in 2012 in London, UK, and is backed by Abingworth, Clarus Ventures and Royalty Pharma.

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Important BOSULIF® (bosutinib) Safety Information

Contraindication: History of hypersensitivity to BOSULIF. Reactions have included anaphylaxis. Anaphylactic shock occurred in less than 0.2% of treated patients in single-agent cancer studies with BOSULIF.

Gastrointestinal Toxicity: Diarrhea, nausea, vomiting, and abdominal pain can occur. In the Phase 3 clinical trial of 268 patients with newly diagnosed CML in the bosutinib treatment group, the median time to onset for diarrhea (all grades) was 3 days and the median duration per event was 3 days. Among 546 patients in a single-arm Phase 1/2 study in patients with CML who were resistant or intolerant to prior therapy, the median time to onset for diarrhea (all grades) was 2 days, median duration was 2 days, and median number of episodes per patient was 3 (range 1-268). Monitor and manage patients using standards of care, including antidiarrheals, antiemetics, and/or fluid replacement. Withhold, dose reduce, or discontinue BOSULIF as necessary.

Myelosuppression: Thrombocytopenia, anemia, and neutropenia can occur. Perform complete blood counts weekly for the first month and then monthly thereafter, or as clinically indicated. Withhold, dose reduce, or discontinue BOSULIF as necessary.

Hepatic Toxicity: Elevations in serum transaminases (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)), can occur. Liver enzyme elevation usually occurs early in treatment. Perform hepatic enzyme tests at least monthly for the first 3 months and as clinically indicated. In patients with transaminase elevations, monitor liver enzymes more frequently. One case consistent with drug-induced liver injury occurred in a trial of BOSULIF in combination with letrozole without alternative causes. Withhold, dose reduce, or discontinue BOSULIF as necessary. In patients with mild, moderate, or severe hepatic impairment, the recommended starting dose is 200 mg daily.

Renal Toxicity: An on-treatment decline in estimated glomerular filtration rate has occurred in patients treated with BOSULIF. Monitor renal function at baseline and during therapy, with particular attention to patients with preexisting renal impairment or risk factors for renal dysfunction. Consider dose adjustment in patients with baseline and treatment emergent renal impairment.

The recommended starting doses for newly diagnosed chronic phase Ph+ CML patients with severe renal impairment (CrCL <30 mL/min) or moderate renal impairment (CrCL 30-50 mL/min) are 200 mg and 300 mg daily, respectively.

The recommended starting doses for chronic, accelerated, or blast phase Ph+ CML patients with resistance or intolerance to prior therapy with severe renal impairment (CrCL <30 mL/min) or moderate renal impairment (CrCL 30-50 mL/min) are 300 mg and 400 mg daily, respectively.

Fluid Retention: Fluid retention can occur with BOSULIF and may cause pericardial effusion, pleural effusion, pulmonary edema, and/or peripheral edema. Among 546 patients in a single-arm Phase 1/2 study in patients with Ph+ CML who were resistant or intolerant to prior therapy, Grade 3/4 fluid retention was reported in 26 patients (5%). Monitor and manage patients using standards of care. Interrupt, dose reduce, or discontinue BOSULIF as necessary.

Embryofetal Toxicity: BOSULIF can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised of the potential hazard to the fetus. Advise females of reproductive potential to use effective contraceptive measures to prevent pregnancy while being treated with BOSULIF and for at least 30 days after the final dose.

Adverse Reactions: The most common adverse reactions observed in greater than or equal to 20% of patients with newly diagnosed CML were diarrhea, nausea, thrombocytopenia, increased ALT, rash, abdominal pain, and increased AST. The most common Grade 3/4 adverse reactions and laboratory abnormalities observed in greater than 10% of newly diagnosed CML patients were thrombocytopenia and increased ALT.

The most common adverse reactions observed in greater than or equal to 20% of patients with CML who were resistant or intolerant to prior therapy were diarrhea, nausea, abdominal pain, thrombocytopenia, rash, vomiting, anemia, fatigue, pyrexia, cough, headache, and ALT. The most common Grade 3/4 adverse reactions and laboratory abnormalities observed in greater than 10% of patients who were resistant or intolerant to prior therapy were thrombocytopenia, neutropenia, and anemia.

CYP3A Inhibitors and Inducers: Avoid concurrent use with strong or moderate CYP3A inhibitors or inducers.

Proton Pump Inhibitors: Consider using short-acting antacids or H2 blockers instead of PPIs to avoid a reduction in BOSULIF exposure. Separate antacid or H2 blocker dosing and BOSULIF dosing by more than 2 hours.

Lactation: Given the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or BOSULIF, taking into account the importance of the drug to the mother.

Please see full Prescribing Information at www.bosulif.com