Syndax Announces FDA Approval of Revuforj® (revumenib), the First and Only Menin Inhibitor to Treat Adult and Pediatric Patients with Relapsed or Refractory Acute Leukemia with a KMT2A Translocation

November 15, 2024

– Approval based on positive data from the AUGMENT-101 clinical trial, in which Revuforj delivered robust and durable rates of remission in R/R acute leukemia patients with a KMT2A translocation –

– Syndax to host conference call today at 6:00 p.m. ET –

WALTHAM, Mass., Nov. 15, 2024 /PRNewswire/ -- Syndax Pharmaceuticals (Nasdaq: SNDX) today announced that the U.S. Food and Drug Administration (FDA) has approved Revuforj® (revumenib) as the first and only menin inhibitor for the treatment of relapsed or refractory (R/R) acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients one year and older. The FDA previously granted Breakthrough Therapy and Fast Track designations as well as Priority Review for Revuforj. The New Drug Application (NDA) received approval through the FDA's Real Time Oncology Review (RTOR) program.

"The approval of Revuforj is a remarkable achievement that reflects the dedication and tenacity of everyone involved, especially the patients and clinicians who participated in our trial and our talented Syndax team," said Michael A. Metzger, Chief Executive Officer of Syndax. "We are well-prepared to launch Revuforj this month and we are committed to rapidly advancing the development of Revuforj across the treatment continuum for KMT2A-rearranged acute leukemias and mutant NPM1 AML."

The efficacy evaluation of Revuforj was based on an FDA analysis of 104 patients with R/R acute leukemia with a KMT2A translocation who were treated with Revuforj in the Phase 1/2 AUGMENT-101 trial. In the efficacy population, the rate of complete remission (CR) plus CR with partial hematological recovery (CRh) was 21% (22/104 pts; 95% CI: 13.8%, 30.3%). The median duration of CR+CRh was 6.4 months (95% CI: 2.7, not estimable) and the median time to CR or CRh was 1.9 months (range: 0.9, 5.6 months). Twenty-three percent (24/104 pts) of patients underwent hematopoietic stem cell transplantation (HSCT) following treatment with Revuforj. Results from the 104-patient efficacy analysis are consistent with the previously reported, protocol-defined Phase 2 interim analysis of patients with R/R KMT2Ar acute leukemia in the AUGMENT-101 trial (n=57) which were published in the *Journal of Clinical Oncology*[1].

"The FDA approval of the first menin inhibitor is a major breakthrough for patients with R/R acute leukemia with a KMT2A translocation, a genetic alteration associated with a very poor prognosis," said Ghayas C. Issa, M.D., Associate Professor of Leukemia at The University of Texas MD Anderson Cancer Center. "The significant clinical benefit and robust efficacy seen with Revuforj represents a substantial improvement over what has been historically observed in these patients with previously available therapies and has the potential to be an important new treatment option for patients."

The safety evaluation of Revuforj was based on an FDA analysis of 135 patients with R/R acute leukemia with a KMT2A translocation who were treated with Revuforj. The most common adverse reactions (≥20%) including laboratory abnormalities were hemorrhage, nausea, phosphate increased, musculoskeletal pain, infection, aspartate aminotransferase increased, febrile neutropenia, alanine aminotransferase increased, parathyroid hormone intact increased, bacterial infection, diarrhea, differentiation syndrome, electrocardiogram QT prolonged, phosphate decreased, triglycerides increased, potassium decreased, decreased appetite, constipation, edema, viral infection, fatigue, and alkaline phosphatase increased. Adverse reactions leading to dose reduction or permanent discontinuation were low at 10% and 12% of patients, respectively.

Rearrangements of the KMT2A gene (KMT2Ar) give rise to an aggressive form of acute leukemia that is associated with a very poor prognosis and high relapse rates.[2] It is estimated that more than 95% of patients with KMT2Ar acute leukemia have a KMT2A translocation, a type of rearrangement that occurs when part of one chromosome breaks and fuses to a different chromosome.[3] More than half of patients with KMT2Ar acute leukemia will relapse after receiving conventional frontline therapies, with a median overall survival (OS) of less than one year.[4] With third line treatment or beyond, only 5% of patients achieve complete remission, and the median OS is less than three months.[4]

Syndax expects that the 110 and 160 mg tablets of Revuforj will be available for order in the United States through a network of specialty distributors and specialty pharmacies in November. Syndax expects that the 25 mg tablets, which may be used to treat patients who weigh less than 40 kg, will be commercially available in late first quarter or early second quarter of 2025. Prior to commercial availability of the 25 mg tablets, an oral solution of revumenib will be available through an expanded access program to allow for dosing of patients who weigh less than 40 kg.

Syndax is committed to supporting patients and removing barriers to access. As part of that commitment, Syndax has established SyndAccess™, a robust program that offers personalized support and resources to U.S. patients who are prescribed Revuforj, including financial assistance for eligible patients. For more information, visit SyndAccess.com or call 1-888-567-SYND (7963), Monday-Friday, 9:00 AM to 6:00 PM Eastern Time (ET).

Conference Call and Webcast

Syndax will host a conference call and webcast to discuss the FDA approval of Revuforj today, November 15, 2024, at 6:00 p.m. ET.

The live webcast may be accessed through the Events & Presentations page in the Investors section of the Company's website. Alternatively, the conference call may be accessed through the following:

Conference ID: Syndax Conference Call 2
U.S. and Canada: (800) 590-8290
International: (240) 690-8800
Webcast URL: https://www.veracast.com/webcasts/syndax/events/specialconf2.cfm

For those unable to participate in the conference call or webcast, a replay will be available on the Investors section of the Company's website at www.syndax.com approximately 24 hours after the conference call and will be available for 90 days following the call.

About Revuforj® (revumenib)

Revuforj (revumenib) is an oral, first-in-class menin inhibitor that is FDA approved for the treatment of relapsed or refractory (R/R) acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients one year and older.

Revumenib is in development for the treatment of R/R acute myeloid leukemia (AML) with a nucleophosmin 1 mutation (mNPM1). Positive pivotal data from the AUGMENT-101 trial in this population with revumenib as a monotherapy were recently reported. Additionally, multiple trials of revumenib in combination with standard-of-care agents in mNPM1 AML or KMT2A-rearranged acute leukemia are ongoing across the treatment landscape, including in newly diagnosed patients.

Revumenib was previously granted Orphan Drug Designation for the treatment of AML, ALL and acute leukemias of ambiguous lineage (ALAL) by the U.S. FDA and for the treatment of AML by the European Commission. The U.S. FDA also granted Fast Track designation to revumenib for the treatment of adult and pediatric patients with R/R acute leukemias harboring a KMT2A rearrangement or NPM1 mutation and Breakthrough Therapy Designation for the treatment of adult and pediatric patients with R/R acute leukemia harboring a KMT2A rearrangement.

IMPORTANT SAFETY INFORMATION

WARNING: DIFFERENTIATION SYNDROME

Differentiation syndrome, which can be fatal, has occurred with Revuforj. Signs and symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, and renal dysfunction. If differentiation syndrome is suspected, immediately initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

WARNINGS AND PRECAUTIONS

Differentiation syndrome: Revuforj can cause fatal or life-threatening differentiation syndrome (DS). Symptoms of DS, including those seen in patients treated with Revuforj, include fever, dyspnea, hypoxia, peripheral edema, pleuropericardial effusion, acute renal failure, and/or hypotension. In clinical trials, DS occurred in 39 (29%) of 135 patients treated with Revuforj. DS was Grade 3 or 4 in 13% of patients and fatal in one. The median time to onset was 10 days (range 3-41 days). Some patients experienced more than 1 DS event. Treatment interruption was required for 7% of patients, and treatment was withdrawn for 1%.

Reduce the white blood cell count to less than 25 Gi/L prior to starting Revuforj. If DS is suspected, immediately initiate treatment with systemic corticosteroids (e.g., dexamethasone 10-mg IV every 12 hours in adults or dexamethasone 0.25-mg/kg/dose IV every 12 hours in pediatric patients weighing less than 40 kg) for a minimum of 3 days and until resolution of signs and symptoms. Institute supportive measures and hemodynamic monitoring until improvement. Interrupt Revuforj if severe signs and/or symptoms persist for more than 48 hours after initiation of systemic corticosteroids, or earlier if life-threatening symptoms occur such as pulmonary symptoms requiring ventilator support. Restart steroids promptly if DS recurs after tapering corticosteroids.

QTc interval prolongation: In the clinical trials, QTc interval prolongation was reported as an adverse reaction in 39 (29%) of 135 patients treated with Revuforj. QTc interval prolongation was Grade 3 in 12% of patients. The heart-rate corrected QT interval (using Fridericia's method) (QTcF) was greater than 500 msec in 8%, and the increase from baseline QTcF was greater than 60 msec in 18%. Revuforj dose reduction was required for 5% of patients due to QTc interval prolongation. QTc prolongation occurred in 16% of the 31 patients less than 17 years old, 33% of the 88 patients 17 years to less than 65 years old, and in 50% of the 16 patients 65 years or older.

Correct electrolyte abnormalities, including hypokalemia and hypomagnesemia, prior to treatment with Revuforj. Perform an electrocardiogram (ECG) prior to initiation of Revuforj, and do not initiate Revuforj in patients with QTcF >450 msec. Perform an ECG at least once weekly for the first 4 weeks and at least monthly thereafter. In patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval, more frequent ECG monitoring may be necessary. Concomitant use with drugs known to prolong the QTc interval may increase the risk of QTc interval prolongation.

- Interrupt Revuforj if QTcF increases >480 msec and <500 msec, and restart Revuforj at the same dose twice daily after the QTcF interval returns to ≤480 msec
- Interrupt Revuforj if QTcF increases >500 msec or by >60 msec from baseline, and restart Revuforj twice daily at the lower-dose level after the QTcF interval returns to ≤480 msec
- Permanently discontinue Revuforj in patients with ventricular arrhythmias and in those who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

Embryo-fetal toxicity: Revuforj can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Revuforj and for 4 months after the last dose of Revuforj.

ADVERSE REACTIONS

Fatal adverse reactions occurred in 4 (3%) patients who received Revuforj, including 2 with differentiation syndrome, 1 with hemorrhage, and 1 with sudden death.

Serious adverse reactions were reported in 99 (73%) patients. The most frequent **serious adverse reactions** (≥5%) were infection (24%), febrile neutropenia (19%), bacterial infection (17%), differentiation syndrome (12%), hemorrhage (9%), and thrombosis (5%).

The most **common adverse reactions** (≥20%) including laboratory abnormalities, were hemorrhage (53%), nausea (51%), phosphate increased (50%), musculoskeletal pain (42%), infection (41%), aspartate aminotransferase increased (37%), febrile neutropenia (35%), alanine aminotransferase increased (33%), parathyroid hormone intact increased (33%), bacterial infection (31%), diarrhea (30%), differentiation syndrome (29%), electrocardiogram QT prolonged (29%), phosphate decreased (25%), triglycerides increased (25%), potassium decreased (24%), decreased appetite (24%), constipation (23%), edema (23%), viral infection (23%), fatigue (22%), and alkaline phosphatase increased (21%).

DRUG INTERACTIONS
Drug interactions can occur when Revuforj is concomitantly used with:

- Strong CYP3A4 inhibitors: reduce Revuforj dose
- Strong or moderate CYP3A4 inducers: avoid concomitant use with Revuforj
- QTc-prolonging drugs: avoid concomitant use with Revuforj. If concomitant use is unavoidable, obtain ECGs when initiating, during concomitant use, and as clinically indicated. Withhold Revuforj if the QTc interval is >480 msec. Restart Revuforj after the QTc interval returns to ≤480 msec.

SPECIFIC POPULATIONS
Lactation: advise lactating women not to breastfeed during treatment with Revuforj and for 1 week after the last dose.

Pregnancy and testing: Revuforj can cause fetal harm when administered to a pregnant woman. Verify pregnancy status in females of reproductive potential within 7 days prior to initiating Revuforj.

Pediatric: monitor bone growth and development in pediatric patients.

Geriatric: compared to younger patients, the incidences of QTc prolongation and edema were higher in patients 65 years and older.

Infertility: based on findings in animals, Revuforj may impair fertility. The effects on fertility were reversible.

To report SUSPECTED ADVERSE REACTIONS, contact Syndax Pharmaceuticals at 1-888-539-3REV or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Full Prescribing Information, including BOXED WARNING.

About KMT2A-Rearranged Acute Leukemia

Rearrangements of the KMT2A gene (KMT2Ar) give rise to an aggressive form of acute leukemia that is associated with a very poor prognosis and high relapse rates.[2] It is estimated that more than 95% of patients with KMT2Ar acute leukemia have a KMT2A translocation, a type of rearrangement that occurs when part of one chromosome breaks and fuses to a different chromosome.[3]

In KMT2Ar acute leukemias, binding of KMT2A fusion proteins with the protein called menin drives the activation of a leukemogenic transcriptional pathway. Inhibition of the menin-KMT2A interaction has been shown to alter the transcription of multiple genes including differentiation markers. KMT2Ar AML and ALL have a rapid onset and quick progression that makes early identification of a KMT2A rearrangement critical.[4,5] It is routinely diagnosed through currently available cytogenetic or molecular diagnostic techniques.

About Syndax

Syndax Pharmaceuticals is a commercial-stage biopharmaceutical company developing an innovative pipeline of cancer therapies. Highlights of the Company's pipeline include Revuforj® (revumenib), an FDA-approved menin inhibitor, and Niktimvo™ (axatilimab-csfr), an FDA-approved monoclonal antibody that blocks the colony stimulating factor 1 (CSF-1) receptor. Fueled by our commitment to reimagining cancer care, Syndax is working to unlock the full potential of its pipeline and is conducting several clinical trials across the continuum of treatment. For more information, please visit www.syndax.com/ or follow the Company on X (formerly Twitter) and LinkedIn.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Words such as "anticipate," "believe," "could," "estimate," "expects," "intend," "may," "plan," "potential," "predict," "project," "should," "will," "would" or the negative or plural of those terms, and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) are intended to identify forward-looking statements. These forward-looking statements are based on Syndax's expectations and assumptions as of the date of this press release. Each of these forward-looking statements involves risks and uncertainties. Actual results may differ materially from these forward-looking statements. Forward-looking statements contained in this press release include, but are not limited to, statements about the progress, timing, clinical development and scope of clinical trials, the reporting of clinical data for Syndax's product candidates, the acceptance of Syndax and its partners' products in the marketplace, sales, marketing, manufacturing and distribution requirements, and the potential use of its product candidates to treat various cancer indications and fibrotic diseases. Many factors may cause differences between current expectations and actual results, including: unexpected safety or efficacy data observed during preclinical or clinical trials; clinical trial site activation or enrollment rates that are lower than expected; changes to Revuforj's commercial availability, changes in expected or existing competition; changes in the regulatory environment; failure of Syndax's collaborators to support or advance collaborations or product candidates; and unexpected litigation or other disputes. Other factors that may cause Syndax's actual results to differ from those expressed or implied in the forward-looking statements in this press release are discussed in Syndax's filings with the U.S. Securities and Exchange Commission, including the "Risk Factors" sections contained therein. Except as required by law, Syndax assumes no obligation to update any forward-looking statements contained herein to reflect any change in expectations, even as new information becomes available.

References

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2. Issa, GC, et al. Therapeutic implications of menin inhibition in acute leukemias. Leukemia 35, 2482–2495 (2021).
3. Meyer, C, et al. The KMT2A recombinome of acute leukemias in 2023. Leukemia 37, 988–1005 (2023).
4. Issa GC, et al. Predictors of outcomes in adults with acute myeloid leukemia and KMT2A rearrangements. Blood Cancer J. 2021;11:162.
5. Nguyen D, et al. Early mortality in acute myeloid leukemia with KMT2A rearrangement is associated with high risk of bleeding and disseminated intravascular coagulation. Cancer. 2023;129(12):1856-1865.

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