

Revumenib

Category:

Best Product for Orphan/Rare Diseases

Company Name:

Syndax

Product/Solution Name:

Revumenib

Compound/Tech Name:

SNDX-5613

Trade Name:

REVUFORJ®

Corporate Name:

Syndax Pharmaceuticals, Inc.

Date of Approval:

2024-11-15

Indications:

REVUFORJ® (revumenib) is a first-in-class, oral, potent, and selective menin inhibitor approved in the United States for the treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A (KMT2A) gene translocation in adult and pediatric patients ≥ 1 year.¹

Revumenib has been granted Orphan Drug designation for the treatment of acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and acute leukemias of ambiguous lineage by the US Food and Drug Administration (FDA).²

Therapeutic Areas:

Acute Leukemias

Acute leukemias are rapidly progressing, malignant clonal disorders marked by uncontrolled proliferation of abnormal and undifferentiated hematopoietic cells in the bone marrow.⁴ They arise from genetic alterations in hematopoietic cells and, if untreated, are often fatal within months.⁵ Patients commonly present with cytopenias, leading to infections, bruising/bleeding, and weakness.⁶⁻⁸ Classification of acute leukemia is based on the origin of the abnormal hematopoietic cells involved, including myeloid, lymphoid, mixed, or undifferentiated cells.⁴ Acute leukemia is broadly classified into 2 main types: AML and ALL; both of which progress rapidly and require prompt treatment.

AML is more common in adults, especially older adults, and results from the uncontrolled proliferation of immature myeloid cells. In 2025, it is estimated that 22,010 individuals in the United States will receive an AML diagnosis, with an estimated 11,090 deaths from the disease.⁹ The overall 5-year relative survival rate (based on data from 2015-2021) is 32.9% but varies considerably across age groups, with older patients having the worst prognosis.^{9,10} The median age at diagnosis is 69 years, with 4.1% of new AML cases diagnosed in people aged <20 years.⁹

ALL results from uncontrolled proliferation of immature lymphoid cells and is more common in younger individuals, with most new cases (52.7%) diagnosed in people aged <20 years (median age at diagnosis: 17 years). In 2025, it is estimated that 6100 individuals in the United States will receive an ALL diagnosis, with 1400 estimated deaths from the disease. The overall 5-year relative survival rate (based on data from 2015-2021) is higher than AML at 72.6%.¹¹

Mixed phenotype acute leukemia (MPAL) is characterized by the presence of biphenotypic or bilineal blast populations of both myeloid and lymphoid origin.¹² MPAL accounts for 1% to 3% of acute leukemias in adults and <5% of pediatric acute leukemias.^{12,13} Based on the phenotypic and genetic diversity of MPAL, treatment resistance, and the potential for lineage switch, MPAL is difficult to treat and confers the worst prognosis among acute leukemias.^{13,14}

KMT2A Rearrangement in Acute Leukemias

Rearrangements (primarily chromosomal translocations)¹⁵ of the KMT2A gene located at chromosome locus 11q23 (hereafter referred to as KMT2Ar) occur in up to 10% of acute leukemias. While the incidence of KMT2Ar varies by age and classification of leukemia, this gene mutation is more prominent in infants (birth to 1 year of age; Figure 1)¹⁵⁻¹⁹ and is associated with drug resistance and poor prognosis.^{15,16,19-23} Based on the 2022 European LeukemiaNet risk classification, the presence of KMT2Ar at diagnosis indicates intermediate/adverse risk.²⁴

Summary

Acute leukemias comprise a heterogeneous group of aggressive malignancies arising from myeloid and/or lymphoid lineages. KMT2Ar is the primary mutation in infants but

occurs in patients of all ages. Based on the adverse prognosis in KMT2Ar-driven acute leukemias, novel therapeutic approaches that target this leukemia-defining genetic abnormality are needed.

General Information File Document upload:

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Background information and need for drug / device:

Existing treatment options/landscape

The current standard of care for acute leukemia involves a multiphase approach primarily centered around chemotherapy followed by stem-cell transplant (SCT). To improve patient outcomes and limit toxicities, research has focused on understanding the genetic drivers of acute leukemia to develop targeted molecular agents.

For AML, several therapies have been approved during the past decade, including those targeting FLT3 (midostaurin, gilteritinib fumarate, and quizartinib dihydrochloride),²⁵⁻²⁷ IDH1 (olutasidenib and ivosidenib),^{28,29} IDH2 (enasidenib mesylate),³⁰ and BCL-2 (venetoclax).³¹ However, while these novel therapies have been approved for adult patients with AML, conventional chemotherapy and allogeneic SCT remain a standard of care for both adult and pediatric patients despite their associated toxicities and risk of relapse.^{24,32,33}

For patients with ALL, targeted therapies, including tyrosine kinase inhibitors for patients with Philadelphia chromosome positive ALL (imatinib, dasatinib, and ponatinib)³⁴⁻³⁶ and immunotherapies for patients with B-cell ALL, such as bispecific antibodies (blinatumomab for CD19-positive B-cell ALL),³⁷ antibody-drug conjugates (inotuzumab ozogamicin for CD22-positive B-cell ALL),³⁸ and CAR T-cell therapy (obecabtagene autoleucel, tisagenlecleucel, and brexucabtagene autoleucel)³⁹⁻⁴¹ are used to address specific genetic abnormalities. Nevertheless, adult patients typically receive a personalized chemotherapy regimen and those with a high risk of relapse also typically receive SCT.⁴² In addition, imatinib and dasatinib (tyrosine kinase inhibitors) are approved in combination with chemotherapy in pediatric patients with newly diagnosed Philadelphia chromosome positive ALL,^{34,35} and blinatumomab, inotuzumab ozogamicin, and tisagenlecleucel (immunotherapies) are approved in pediatric patients with B-cell ALL.^{37,38,40} Despite these approvals, pediatric patients with ALL also typically receive chemotherapy as standard-of-care treatment.⁴³

For KMT2Ar acute leukemia, most patients receive conventional chemotherapy or venetoclax combinations, with an allogeneic hematopoietic SCT in consolidation, and experience suboptimal outcomes.²¹ Despite advances in the treatment of pediatric acute leukemia, infant KMT2A-translocated acute leukemias have remained a

therapeutic challenge due to high rates of resistance to multiagent chemotherapy.^{44,45}

Unmet need

Relapsed or refractory KMT2Ar acute leukemia has a poor prognosis, and available treatments fall short in targeting this leukemia-defining genetic abnormality, yielding suboptimal response rates that lack durability, while also carrying significant toxicity risks. Moreover, they may trigger lineage-switch events, further complicating patient outcomes.⁴⁶ Given the adverse prognosis in KMT2Ar acute leukemia, there is an urgent need for novel therapies that specifically target this genetic abnormality.

While the prognosis of pediatric AML has improved over the past decade, 25% to 40% of patients will eventually relapse.³² The long-term impact of chemotherapy on children underscores the critical need for targeted therapies that not only enhance survival but also reduce long-term toxicities. However, enrolling pediatric patients in clinical trials presents challenges, and access to innovative therapies remains limited.^{32,47} This highlights a significant unmet need for novel immunotherapies and targeted agents that can further improve outcomes, minimize long-term medical complications and toxicities, and be more readily accessible to a growing population of childhood leukemia survivors.

Background File Document upload:

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History of the development of the solution/product:

Target Identification

Menin, the protein product of the MEN1 tumor suppressor gene, binds KMT2A and drives oncogenesis. Menin dependency occurs in KMT2Ar, NPM1m, and NUP98-rearranged (NUP98r) acute leukemias, and other neoplasms.⁴⁸ In KMT2Ar acute leukemia, the menin-KMT2A interaction upregulates HOX/MEIS gene expression, causing hematopoietic differentiation arrest and leukemogenesis. Preclinical evidence in KMT2Ar xenograft models demonstrates disease eradication with menin inhibition, supporting menin inhibitors as treatment for KMT2Ar leukemias.⁴⁹⁻⁵²

To improve patient outcomes for difficult-to-treat cancers, Syndax is exploring menin-KMT2A inhibition in acute leukemias, including pediatric patients. In just 5 years from Investigational New Drug acceptance to first FDA approval, REVUFORJ® (revumenib) made remarkable strides, driven by dedicated efforts of researchers and clinicians committed to improving treatment options for patients with acute leukemias (Figure 2). This approval represents a major scientific breakthrough for patients.

Mechanism of Action

Revumenib is a first-in-class, oral, potent, and selective menin inhibitor⁵³ that competitively binds a discrete, well-defined pocket within menin where KMT2A-fusion proteins bind, resulting in global loss of menin-chromatin binding (Figure 3).

Menin-KMT2A complex loss from target gene loci reduces transcriptional activity at critical leukemogenic genes, resulting in leukemic cell differentiation and apoptosis.⁵⁴

Clinical Development

Revumenib has a robust clinical development plan with ongoing studies in KMT2Ar, NPM1m, and NUP98r acute leukemias, including the pivotal, first-in-human, registration-enabling AUGMENT-101 study (Figures 4-5).

AUGMENT-101 is a phase 1/2, multicenter, open-label, dose-escalation/expansion study of revumenib in relapsed/refractory KMT2Ar, NPM1m, or NUP98r acute leukemias (NCT04065399; Figure 6).⁵⁵ To date, AUGMENT-101 is the largest evaluation of targeted therapy for relapsed/refractory KMT2Ar acute leukemias and includes the largest cohort of pediatric patients treated with a menin inhibitor.⁵³

Phase 1: Revumenib demonstrated encouraging clinical benefit, including deep molecular remissions and minimal toxicities, among children and adults with heavily pretreated acute leukemia.²⁰ The total population (KMT2Ar or NPM1m) achieved a 53% overall response rate (ORR), with 30% achieving complete remission or complete remission with partial hematologic recovery (CR+CRh). Similar findings were observed in the KMT2Ar-only population (ORR, 59%; CR+CRh, 33%).²⁰ Revumenib demonstrated tolerability, with a low rate of grade ≥ 3 treatment-related adverse events (AEs; 16.2%).²⁰

Phase 2: Revumenib demonstrated high remission rates with a well-characterized safety profile in relapsed/refractory KMT2Ar acute leukemia. At interim analysis (median follow-up, 6.1 months), the study met the primary endpoint (22.8% CR+CRh rate).⁵⁶ With longer follow-up and a larger population, revumenib continued to provide clinically meaningful and durable responses, including high measurable residue disease (MRD)-negativity rates (Figure 7) and feasible SCT for some patients.⁵³ CR+CRh rates were consistent across patient subgroups and KMT2Ar subtypes (Figure 8). No new safety signals were reported (Figure 9), AEs resulting in dose reduction/treatment discontinuation were low, and no patients discontinued treatment due to cytopenias, differentiation syndrome, or QTc prolongation.

Based on AUGMENT-101 data, revumenib received Breakthrough Therapy and Fast Track designation, Orphan Drug designation, and Priority Review, culminating in FDA approval in November 2024, making it the first approved menin inhibitor and first approved treatment for relapsed/refractory acute leukemia with a KMT2A gene translocation in adult and pediatric patients ≥ 1 year.

Development File Document upload:

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Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition:

Revumenib is the first approved treatment for adult and pediatric patients ≥ 1 year with relapsed/refractory acute leukemia with a KMT2A translocation, and its value continues expanding.

Pediatric Acute Leukemia: Historical lag time from first-in-human trial to first pediatric trial is 6.5 years and, from 2008 to 2017, only ~8% of phase 1 or 2 oncology trials were open to both adults and children.⁵⁷ At the time of approval, revumenib became 1 of only 60 FDA-approved drugs in the last 75 years for pediatric cancers.⁵⁸ The phase 1 AUGMENT-102 study evaluated revumenib plus fludarabine/cytarabine in predominantly pediatric patients (74.1% of patients < 18 years) with relapsed/refractory NPM1m, NUP98r, or KMT2Ar AML.⁵⁹ No new safety concerns were identified, and deep responses were observed, with composite complete remission (CRc) achieved in 56% and 50% of patients treated with revumenib 113 and 163 mg, respectively. Among those who achieved CRc, 71% achieved MRD negativity.⁵⁹

Data from AUGMENT-101 demonstrate the clinical efficacy of revumenib monotherapy, and AUGMENT-102 data highlight its potential in combination with fludarabine/cytarabine for pediatric patients who desperately need effective and tolerable treatments. Additional studies supporting revumenib monotherapy and combination regimens in pediatric patients with newly diagnosed or relapsed/refractory acute leukemia are ongoing or planned.

NPM1m: NPM1m is the most common genetic alteration in adult AML (~30% of cases).^{60,61} Patients with relapsed/refractory NPM1m AML have poor prognosis and high unmet need, with no approved targeted therapies. Topline data from AUGMENT-101 demonstrated efficacy, with no new safety concerns in relapsed/refractory NPM1m AML.^{60,61} The study met its primary endpoint (CR+CRh rate, 23%). A supplemental New Drug Application for relapsed/refractory NPM1m AML is under Priority Review as of June 2025. Revumenib may significantly impact the ~40% of patients with acute leukemias harboring NPM1m or KMT2Ar.

Combinability: Early data suggest revumenib-based therapy is feasible and appealing due to its mechanism of action, opportunities for synergy, and safety profile. Preclinical data and the clinical safety profile highlight the potential to form combinations with

partner agents, including standard-of-care chemotherapy, BCL-2 or FLT3 inhibitors, or other therapies.⁶²

Preliminary results of the phase 1/2 SAVE study investigating revumenib plus decitabine/cedazuridine/venetoclax in children and adults with relapsed/refractory KMT2Ar, NPM1m, or NUP98 AML indicate a consistent safety profile and promising efficacy (ORR, 82%; MRD-negativity rate, 65%).⁶³ Encouraging data were also observed in the phase 1b dose-escalation/expansion BEAT-AML study of revumenib plus azacitidine/venetoclax in newly diagnosed patients aged ≥ 60 years with NPM1m or KMT2Ar AML.⁶⁴ Deep responses were seen (CRc rate, 96%; MRD-negativity rate, 92%),⁶⁴ and dose expansion is ongoing. The randomized phase 3 EVOLVE-2/HO177/AMLSG35-24/ACT-HOV-AML-002 study of revumenib plus azacitidine/venetoclax is enrolling (NCT06652438). Additional ongoing and planned studies are investigating revumenib-based combinations in KMT2Ar, NPM1m, and NUP98r acute leukemias.

Revumenib's proven efficacy in acute leukemias, including KMT2Ar and NPM1m genetic alterations, and in pediatric patients underscores its innovative contribution to advancing the field. Its targeted mechanism, convenient oral formulation, well-tolerated safety profile, and versatility as a potential combination therapy, enhance its overall therapeutic value and position revumenib as a groundbreaking advancement for menin-sensitive acute leukemias.

Innovation File Document upload:

N/A

Please provide appropriate references (PubMed, Abstract, Website):

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