RETHYMIC®
allogeneic processed thymus tissue-agdc

HELP YOUR PEDIATRIC PATIENTS
WITH CONGENITAL ATHYMIA

Discover the wonder of childhood

RETHYMIC is a first-of-its-kind, FDA-approved tissue-based treatment for congenital athymia engineered to help patients develop an immune system sufficient to fight infections.[1,2]

Indication

RETHYMIC® (allogeneic processed thymus tissue–agdc) is indicated for immune reconstitution in pediatric patients with congenital athymia.

Limitations of Use:
RETHYMIC is not indicated for the treatment of patients with severe combined immunodeficiency (SCID).

Important Safety Information

Immune reconstitution sufficient to protect from infection is unlikely to develop prior to 6-12 months after treatment with RETHYMIC. Given the immunocompromised condition of athymic patients, follow infection control measures until the development of thymic function is established as measured through flow cytometry. Monitor patients closely for signs of infection including fever. If a fever develops, assess the patient by blood and other cultures and treat with antimicrobials as clinically indicated. Patients should be maintained on immunoglobulin replacement therapy until specified criteria are met, and two months after stopping, IgG trough level should be checked. Prior to and after treatment with RETHYMIC, patients should be maintained on *Pneumocystis jiroveci* pneumonia prophylaxis until specified criteria are met.

Please see additional Important Safety Information and the QR code to the full Prescribing Information on pages 14 & 15, or visit RETHYMIC.com/prescribing-information.

Brynlee, a patient with congenital athymia.

Scan the QR code to learn about our patient support program, or visit EnzyvantCONNECT.com

About RETHYMIC

RETHYMIC is a first-of-its-kind, FDA-approved tissue-based treatment for congenital athymia[1,2]

RETHYMIC is a one-time treatment that is engineered to help patients with congenital athymia develop an immune system sufficient to fight infections.[1,2]

Unlike a transplant, RETHYMIC is engineered donor thymus tissue manufactured during a 12- to 21-day process. RETHYMIC is implanted in the thigh muscle via a single surgical procedure.[1]

Important Safety Information (cont'd)

RETHYMIC may cause or exacerbate pre-existing graft versus host disease (GVHD). Monitor and treat patients at risk for the development of GVHD. Risk factors for GVHD include atypical complete DiGeorge anomaly phenotype, prior hematopoietic cell transplantation (HCT) and maternal engraftment. GVHD may manifest as fever, rash, lymphadenopathy, elevated bilirubin and liver enzymes, enteritis, and/or diarrhea.

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How RETHYMIC works

The proposed mechanism of action involves the migration of the patient's T-cell progenitors to RETHYMIC where they develop into T cells that are sufficient to fight infections.[1]

Evidence of thymic function may be observed with this development in the peripheral blood. However, immune reconstitution sufficient to protect against infection is unlikely to develop prior to 6 to 12 months after treatment with RETHYMIC.[1]

About congenital athymia

Congenital athymia is a rare immune condition that causes life-threatening immunodeficiency and immune dysregulation. It is characterized by the lack of a thymus at birth, leading to an increased susceptibility to life-threatening infections and autoimmune conditions.[3,4]

Important Safety Information (cont'd)

Autoimmune-related adverse events occurred in patients treated with RETHYMIC. These events included: thrombocytopenia, neutropenia, proteinuria, hemolytic anemia, alopecia, hypothyroidism, autoimmune hepatitis, autoimmune arthritis, transverse myelitis, albinism, hyperthyroidism, and ovarian failure. Monitor for the development of autoimmune disorders, including complete blood counts with differential, liver enzymes, serum creatinine, urinalysis, and thyroid function.

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RETHYMIC greatly improved survival for patients with congenital athymia[1]

The efficacy and safety of RETHYMIC were evaluated in **105 pediatric patients across 10 open-label, prospective, single-center clinical trials,** including 95 patients in the primary efficacy analysis, with a follow-up of up to 25.5 years.[1,4]

Patient demographics[1]

Characteristic		Primary efficacy analysis (N=95)
Median (range) age at the time of treatment, months		9 (1-36)
Male, %		59
Race, %	White	70
	Black	22
	Asian/Pacific Islander	4
	American Indian/Alaskan Native	2
	Multi-race	2
Diagnosed with atypical complete DiGeorge syndrome,* %		44

*These patients may have had a rash, lymphadenopathy, oligoclonal cells.[1]

Important Safety Information (cont'd)

Pre-existing renal impairment is a risk factor for death.

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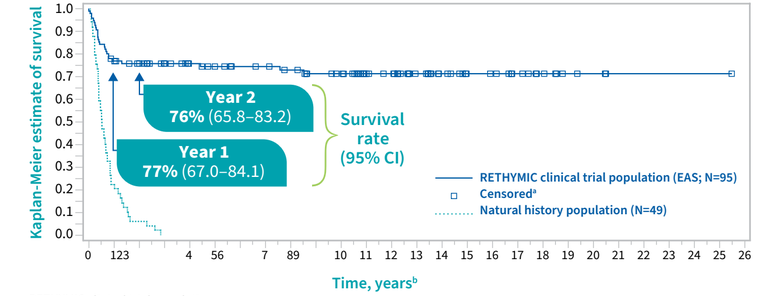
Survival rates

Primary and supportive endpoints: Kaplan-Meier estimated survival rates were 77% (95% CI, 0.679, 0.841) at year 1 and 76% (95% CI, 0.658, 0.832) at year 2[1,4]

Survival by Year[1]



RETHYMIC clinical trial population

At risk	95	95	72	67	62	57	54	50	49	46	42	40	33	31	24	18	13	12	9	6	3	2	1	1	1	1
Events	0	22	1	0	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Natural history population

At risk	49	49	11	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Events	0	38	8	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

[a]Patients were censored at the time of their most recent follow-up for the RETYHMIC clinical trial program. No patients in the natural history population were censored.
[b]Time is years after administration for the RETHYMIC clinical trial population and years of life for the natural history population.

For patients who were alive at 1 year after treatment, the survival rate was

94%

with a median follow-up of 10.7 years[1]

In a natural history study, congenital athymia patients on supportive care alone typically did not survive beyond 2 to 3 years of age.[1]

Important Safety Information (cont'd)

In the clinical studies of RETHYMIC, 4 out of 4 patients with pre-existing cytomegalovirus infection died. The benefits/risks of treatment should be considered prior to treating patients with pre-existing CMV infection.

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Immune system development

Secondary endpoint: Naive CD4$^+$ and CD8$^+$ T cells reconstituted over the first year following treatment and increased through year 2[1,4]

Development of Naive T Cells Following Treatment[1,4]

	Baseline	Month 6	Month 12	Month 24
Median naive CD4$^+$ T cells/mm^3	**1.0**	**42**	**212**	**275**
(min, max)	(0, 38)	(0, 653)	(1, 751)	(33, 858)
Number of subjects	63	62	42	26
Median naive CD8$^+$ T cells/mm^3	**0**	**9**	**58**	**86**
(min, max)	(0, 46)	(0, 163)	(0, 304)	(6, 275)
Number of subjects	60	53	37	26

Immune reconstitution sufficient to protect against infection is unlikely to develop prior to 6 to 12 months after treatment, and for some patients, may take up to 2 years.[1]

Important Safety Information (cont'd)

Because of the underlying immune deficiency, patients who receive RETHYMIC may be at risk of developing post-treatment lymphoproliferative disorder. Patients should be monitored for the development of lymphoproliferative disorder.

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Infection reduction

RETHYMIC significantly decreased the rate of infections in the first 2 years after treatment.[1]

AT 6 TO ≤12 MONTHS AFTER TREATMENT,

38%

fewer patients
experienced an infection event
vs 0 to ≤6 months after treatment (P<0.001)[1]

AT 12 TO ≤24 MONTHS AFTER TREATMENT, THERE WAS A MEAN DIFFERENCE OF

2.9

events per patient
vs 0 to ≤12 months after treatment (P<0.001)[1]

Important Safety Information (cont'd)

Transmission of infectious disease may occur because RETHYMIC is derived from human tissue and because product manufacturing includes porcine- and bovine-derived reagents.

Please see additional Important Safety Information and the QR code to the full Prescribing Information on pages 14 & 15, or visit RETHYMIC.com/prescribing-information.

The safety of RETHYMIC was demonstrated in 105 patients across 10 clinical trials[1]

The most common (≥10%) adverse reactions related to RETHYMIC were hypertension, cytokine release syndrome, hypomagnesemia, rash, renal impairment/failure, thrombocytopenia, and graft versus host disease (GVHD).[1]

Of the 105 patients in clinical studies, 29 patients died. The majority of deaths in the first year after receiving RETHYMIC were due to infections (13).[1]

Scan the QR code to learn more about RETHYMIC, or visit RETHYMIC.com/hcp

Important Safety Information (cont'd)

Immunizations should not be administered in patients who have received RETHYMIC until immune-function criteria have been met.

Adverse reactions occurring in at least 5% of patients in the first 2 years after treatment[1]

System organ class	RETHYMIC (N=105) n (%)
Number of patients with adverse reactions	80 (76)
Hypertension	20 (19)
Cytokine release syndrome All events occurred in association with anti-thymocyte globulin [rabbit] treatment	19 (18)
Hypomagnesemia	17 (16)
Rash, granuloma skin, rash papular, and urticaria	16 (15)
Renal impairment/failure, acute kidney injury, proteinuria, and increased blood creatinine	13 (12)
Thrombocytopenia and immune thrombocytopenic purpura	13 (12)
Graft versus host disease, GVHD-gut, GVHD-skin, and Omenn syndrome	11 (10)
Hemolytic anemia, autoimmune hemolytic anemia, Coombs-positive hemolytic anemia, and hemolysis	9 (9)
Neutropenia	9 (9)
Respiratory distress, hypoxia, and respiratory failure	8 (8)
Proteinuria	7 (7)
Pyrexia	6 (6)
Acidosis, renal tubular acidosis, and decreased blood bicarbonate	6 (6)
Diarrhea and hemorrhagic diarrhea	5 (5)
Seizure, infantile spasms, and febrile convulsions	5 (5)

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Administration and dosage

RETHYMIC is a one-time treatment administered via a single surgical procedure[1,2]

RETHYMIC is implanted in one, or both if necessary, of the patient's thighs during a surgical procedure. RETHYMIC is currently only available at Duke University Health System in Durham, North Carolina.[1,5]

After general anesthesia, a **~5-cm-long vertical incision is made** over the anterior thigh compartment.[1]

Individual slices of RETHYMIC are implanted in created pockets between the muscle fibers.[1]

Each implanted RETHYMIC slice is **fully covered by muscle tissue** and the pockets stitched closed with a single absorbable suture.[1]

The skin incision is closed with absorbable sutures and a standard dressing is applied.[1]

The dosage is determined based on the total surface area of the RETHYMIC tissue slices, and the amount implanted is calculated based on the recipient's body surface area (BSA).[1]

Important Safety Information (cont'd)

All patients should be screened for anti-HLA antibodies prior to receiving RETHYMIC. Patients testing positive for anti-HLA antibodies should receive RETHYMIC from a donor who does not express those HLA alleles. HLA matching is required in patients who have received a prior HCT or a solid organ transplant. Patients who have received a prior HCT are at increased risk of developing GVHD after RETHYMIC if the HCT donor did not fully match the recipient.

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Not an actual patient.

The engineering process

Unlike a transplant, RETHYMIC is engineered for one patient at a time through a complex process using donor thymus tissue[1,6]

Donation of thymus tissue

When an infant ≤9 months of age undergoes cardiac surgery, some thymus tissue may need to be removed to access the heart. **With consent of the infant donor's parents or guardian, the thymus tissue is donated and undergoes extensive testing** to determine the viability and safety of the tissue for making RETHYMIC.[6]

Unlike many other medications or specialty biologics, RETHYMIC is not an off-the-shelf product. **The thymus tissue from a single infant donor allows for the manufacturing of RETHYMIC for one patient.[1]**

The availability of RETHYMIC is largely dependent on the size and viability of the thymus tissue that is donated.[6,7]

Development of RETHYMIC

The time the engineering process takes depends on multiple factors and can be completed between **12 and 21 days.[7]**

RETHYMIC is engineered in a dedicated environment that follows strict FDA requirements. The manufacturing personnel have been extensively trained on proper safety protocols to maintain a sterile environment and avoid cross contamination.

The engineering process requires manufacturing personnel to manually change the media, preserving thymic epithelial cells and tissue structure while depleting most of the donor thymocytes. During this time, **the donor thymus tissue goes through multiple rigorous tests**—some of which are repeated—to ensure the product meets FDA safety standards.[1,7]

Implantation of RETHYMIC

The dosage is determined based on the total surface area of the RETHYMIC tissue slices, and **the amount implanted is calculated based on the recipient's BSA.[1]**

Once released from the manufacturing facility, RETHYMIC must be implanted within a limited time frame at the treatment center.[7]

Careful coordination of the engineering of RETHYMIC must coincide with the preparation of a potential patient to receive the product.[7]

Important Safety Information (cont'd)

Of the 105 patients in clinical studies, 29 patients died, including 23 deaths in the first year (< 365 days) after implantation.

Important Safety Information (cont'd)

The most common (>10%) adverse events related to RETHYMIC included: hypertension, cytokine release syndrome, rash, hypomagnesemia, renal impairment/failure, thrombocytopenia, and graft versus host disease.

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Post-treatment care is critically important[1]

Immune reconstitution sufficient to protect against infection is unlikely to develop prior to 6 to 12 months after treatment. For some patients, it may take up to 2 years.[1]

After treatment with RETHYMIC, patients will return to the care of the referring healthcare provider and should be monitored regularly for autologous GVHD and autoimmune disorders. Tests for monitoring will include/measure[1,6,8]:

- Complete blood count with differential
- Liver enzymes
- Serum creatinine levels
- Urinalysis
- Thyroid function

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Jada, a patient with congenital athymia.

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Relaxing infection prevention measures

Once T cells reach certain levels, additional testing can be done to determine if the patient can discontinue the following[8]:

- Immunosuppressants
- Immunoglobulin replacement therapy
- Antibiotics
- Antifungals

Inactivated and live vaccines should not be administered until requirements outlined in the RETHYMIC Prescribing Information have been met.[1]

It is recommended that careful monitoring and isolation occur to help ensure the patient avoids infection and other complications after treatment. Consider how best to work with the care team and caregiver of your patient to determine what measures can be lifted and when.[1]

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Of the 105 patients in clinical studies, 29 patients died, including 23 deaths in the first year (< 365 days) after implantation.

The most common (>10%) adverse events related to RETHYMIC included: hypertension, cytokine release syndrome, rash, hypomagnesemia, renal impairment/failure, thrombocytopenia, and graft versus host disease.

To report suspected adverse reactions, please contact the FDA at 1-800-FDA-1088 or www.fda.gov/safety/medwatch

References:

1. RETHYMIC [package insert]. Marlborough, MA: Sumitomo Pharma America, Inc; 2023. **2.** Enzyvant Therapeutics GmbH. Enzyvant receives FDA approval for RETHYMIC® (allogeneic processed thymus tissue-agdc), a one-time regenerative tissue-based therapy for pediatric congenital athymia. Enzyvant Therapeutics, Inc. October 8, 2021. Accessed March 3, 2023. https://enzyvant.com/enzyvant-receives-fda-approval-for-rethymic-allogeneic-processed-thymus-tissue-agdc-a-one-time-regenerative-tissue-based-therapy-for-pediatric-congenital-athymia/ **3.** Collins C, Sharpe E, Silber A, Kulke S, Hsieh EWY. Congenital athymia: genetic etiologies, clinical manifestations, diagnosis, and treatment. *J Clin Immunol.* 2021;41(5):881-895. doi:10.1007/s10875-021-01059-7 **4.** Markert ML, Gupton SE, McCarthy EA. Experience with cultured thymus tissue in 105 children. *J Allergy Clin Immunol.* 2022;149(2):747-757. doi:10.1016/j.jaci.2021.06.028 **5.** Hsieh EWY, Kim-Chang JJ, Kulke S, Silber A, O'Hara M, Collins C. Defining the clinical, emotional, social, and financial burden of congenital athymia. *Adv Ther.* 2021;38(8):4271-4288. doi:10.1007/s12325-021-01820-9 **6.** Markert ML. Defects in thymic development. In: Sullivan KE, Stiehm ER, eds. *Stiehm's Immune Deficiencies: Inborn Errors of Immunity.* 2nd ed. Elsevier; 2020:1229-1239. **7.** Food and Drug Administration. Summary Basis for Regulatory Action. October 8, 2021. BLA STN: 125685/0. **8.** Gupton SE, McCarthy EA, Markert ML. Care of children with DiGeorge before and after cultured thymus tissue implantation. *J Clin Immunol*. 2021;41(5):896-905. doi:10.1007/s10875-021-01044-0

Please scan the QR code to see the full Prescribing Information, or visit RETHYMIC.com/prescribing-information

Supporting patients and their families

Enrolling your patients in the Enzyvant CONNECT® Patient Support Program will give their caregivers access to **educational resources** and, if eligible, **financial assistance** as they navigate the congenital athymia journey. Enzyvant CONNECT is available to patients with any type of insurance—including commercial plans, Medicare, or Medicaid—as well as patients who are underinsured or have no insurance coverage.

Dedicated care team

- The Support Liaison will help your patients' caregivers understand their child's diagnosis
- The Access Specialist can help caregivers navigate insurance benefits and financial assistance

Access to exclusive resources

- Document organizer
- *Sadie's Search*, a storybook written specifically with your patient in mind
- Interactive T-cell progress tracker
- Activity book
- And more!

Co-pay program

- The Enzyvant CONNECT® Commercial Co-Pay Program can help caregivers of eligible commercially-insured patients in the US and US territories
- They may receive co-pay assistance for medication-related out-of-pocket costs for a treatment for congenital athymia

Scan the QR code to enroll your patients, or visit EnzyvantCONNECT.com/get-started

Call 844-ENZCNCT (844-369-2628) to connect your patients to personalized support.
Support is available Monday–Friday, 8:00 AM to 8:00 PM ET.

Sumitomo Pharma