HELP YOUR PEDIATRIC PATIENTS
WITH CONGENITAL ATHYMIA

Discover the wonder of childhood

RETHYMIC® allogeneic processed thymus tissue-agdc

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]

RETHYMIC is not indicated for the treatment of patients with severe combined immunodeficiency.[1]

Brynlee, a patient with congenital athymia.

INDICATION

RETHYMIC® 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

Infection Control and Immunoprophylaxis: Immune reconstitution sufficient to protect from infection is unlikely to develop prior to 6-12 months after treatment with RETHYMIC. Follow infection control measures until the development of thymic function is established as measured by flow cytometry. Closely monitor patients for signs of infection. If fever develops, assess the patient via lab results and treat as clinically indicated. Patients should be maintained on immunoglobulin replacement therapy (IgG) and *Pneumocystis jirovecii* pneumonia prophylaxis until specified criteria are met. IgG trough level should be checked 2 months after stopping IgG to determine whether the patient may remain off IgG.

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.

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

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)

Graft versus Host Disease (GVHD): RETHYMIC may cause or exacerbate pre-existing GVHD, for which patients should be closely monitored and treated. Risk factors include atypical complete DiGeorge anomaly phenotype, prior hematopoietic cell transplantation (HCT), and maternal engraftment. Patients with specified elevated baseline T cell proliferative response to PHA should receive immunosuppressants to decrease this risk. 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. 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. It is characterized by the lack of a functioning thymus at birth, leading to an increased susceptibility to life-threatening infections.[3,4]

Jada, a patient with congenital athymia.

IMPORTANT SAFETY INFORMATION (cont'd)

Autoimmune Disorders: 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 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
Associated conditions, %	22q11.2 deletion	38
	CHARGE syndrome	24
	FOXN1 deficiency	2
	TBX variant	1
Diagnosed with complete DiGeorge syndrome, %	Typical	53
	Atypical*	44

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

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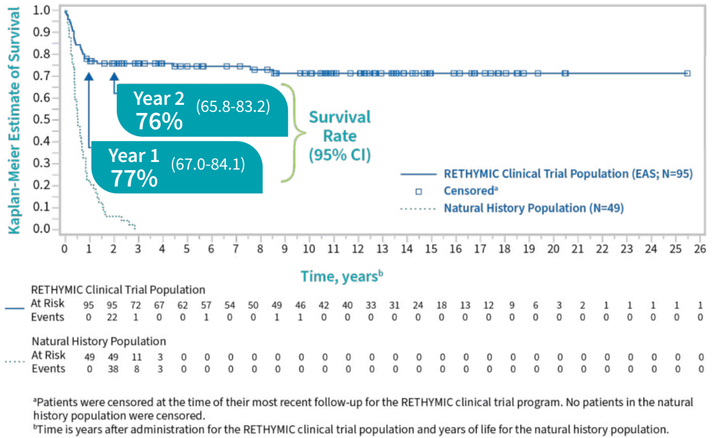
Survival rates

Primary and supportive endpoints: Kaplan-Meier estimated survival rates were 77% (95% CI, 0.670, 0.841) at year 1 and 76% (95% CI, 0.658, 0.832) at year 2[1,4]

Survival by Year[1]



[a]Patients were censored at the time of their most recent follow-up for the RETHYMIC 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)

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

Cytomegalovirus Infection (CMV): In the clinical studies, 4 out of 4 patients with pre-existing CMV infection died.

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/mm³	**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/mm³	**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)

Malignancy: Due to underlying immune deficiency, patients who receive RETHYMIC may be at risk of developing post-treatment lymphoproliferative disorder. Patients should be tested for Epstein-Barr virus and CMV prior to and 3 months after treatment or after any suspected exposure.

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Infection reduction

RETHYMIC significantly decreased the rate of infections in the first 2 years after treatment.[1,4]

AT 6 TO ≤12 MONTHS AFTER TREATMENT,

38%

fewer patients
experienced an infection event
vs 0 to ≤6 months after treatment (P<0.001)[1,4]

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 Serious Infections and Transmissible Infectious Diseases: Transmission of infectious disease may occur because RETHYMIC is derived from human tissue, and 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 died, including 23 in the first year. 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)

Vaccine Administration: Immunizations should not be given in patients treated with RETHYMIC until immune-function criteria have been met. Live virus vaccines should not be given until patients have met the criteria for and received inactivated vaccines.

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 Children's Hospital 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]

This is only an overview of the implantation procedure. Please see the full Prescribing Information for the complete administration instructions.

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)

Anti-HLA Antibodies: All patients should be screened for anti-HLA antibodies prior to receiving RETHYMIC. Patients testing positive should receive RETHYMIC from a donor who does not express those HLA alleles.

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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]

Manufacturing 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)

HLA Typing: HLA matching is required in patients who have received a prior HCT or a solid organ transplant.

IMPORTANT SAFETY INFORMATION (cont'd)

HLA Typing (cont'd): Patients who have received a HCT are at increased risk of developing GVHD after RETHYMIC if the HCT donor does not fully match with RETHYMIC.

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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 with RETHYMIC. 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 autoimmune disorders will include/measure[1,6,8]:

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

IMPORTANT SAFETY INFORMATION (cont'd)

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

Adverse Reactions: The most common (>10%) adverse events included hypertension, cytokine release syndrome, rash, hypomagnesemia, renal impairment/failure, thrombocytopenia, and GVHD.

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 (IgG) replacement therapy
- Antibiotics
- Antifungals

Please refer to the RETHYMIC Prescribing Information for the criteria for the discontinuation of immunosuppressants, IgG therapy, and prophylaxis for *Pneumocystis jirovecii*.

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

Careful monitoring and isolation are required to ensure your patient avoids infections after treatment with RETHYMIC. Your patient should also be monitored for other complications, like GVHD and autoimmune disorders. Consider how best to work with the care teams and caregivers of your patients to determine what measures can be lifted and when.[1]

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References:

1. RETHYMIC [package insert]. Marlborough, MA: Sumitomo Pharma America, Inc; 2023. **2.** Sumitomo Pharma America, Inc. Enzyvant receives FDA approval for RETHYMIC® (allogeneic processed thymus tissue-agdc), a one-time regenerative tissue-based therapy for pediatric congenital athymia. Accessed June 27, 2024. https://www.us.sumitomo-pharma.com/newsroom/press-releases/Enzyvant-Receives-FDA-Approval-for-RETHYMIC-allogeneic-processed-thymus-tissue-agdc-a-One-Time-Regenerative-Tissue-Based-Therapy-for-Pediatric/ **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

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connect

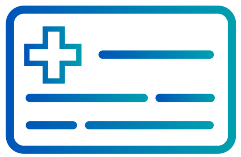
Enrolling your patients in the RETHYMIC Connect™ Patient Support Program will give their caregivers access to **educational resources** and, if eligible, **financial assistance** as they navigate the congenital athymia journey. RETHYMIC Connect is available to patients with any type of insurance—including 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 patients in mind
- Interactive T-cell progress tracker
- Activity book
- And more!



Co-pay program

- The RETHYMIC 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 RETHYMIC

Scan the QR code to enroll your patients, or visit RETHYMIC.com/hcp

Call 877-RETHYMC (877-738-4962) to connect your patients to personalized support.
Support is available Monday–Friday, 8:00 AM to 8:00 PM ET.

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.

Sumitomo Pharma