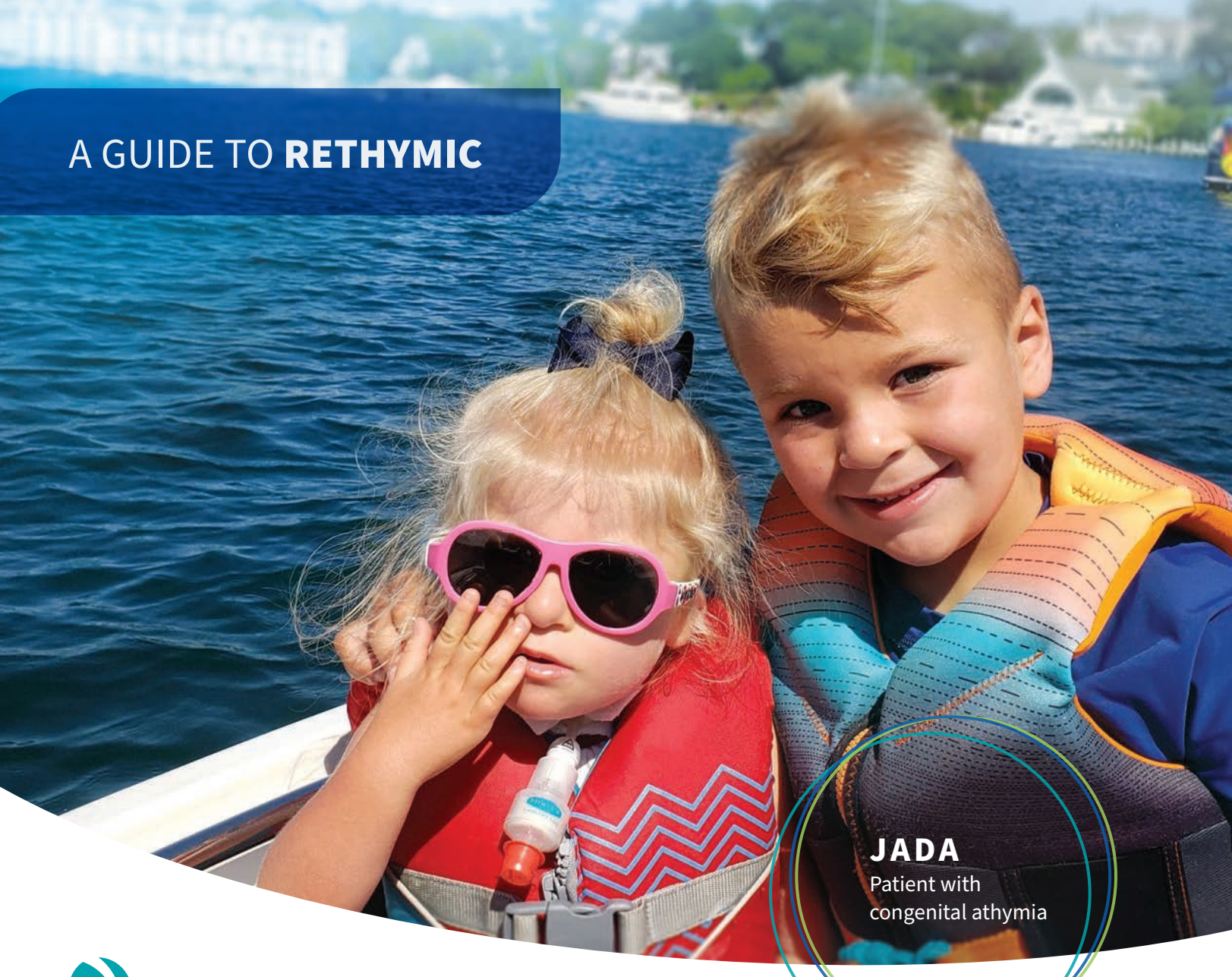
A GUIDE TO **RETHYMIC**



JADA
Patient with
congenital athymia

RETHYMIC®
allogeneic processed
thymus tissue-agdc

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 on pages 14 & 15, and the enclosed full Prescribing Information.

Overview of congenital athymia

Congenital athymia is an ultra-rare condition characterized by the absence of a thymus at birth.[1] Estimated incidence in the United States is approximately 17 to 24 infants for every 4 million live births per year.[2]

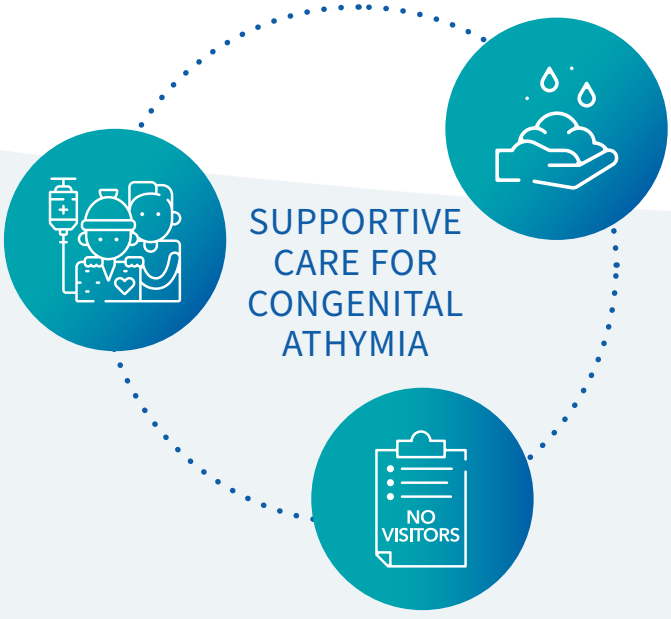
About Congenital Athymia

The thymus is the organ responsible for the development of mature T cells. Infants without a thymus suffer from profound immunodeficiency. Characteristics of congenital athymia include a profound T-cell deficiency, frequent infections, susceptibility to opportunistic infections, and propensity to develop autologous graft versus host disease (GVHD) and autoimmunity, such as thrombocytopenia.[1] Multiple syndromic conditions—such as complete DiGeorge syndrome, 22q11.2 deletion syndrome, CHARGE (coloboma, heart defects, choanal atresia, growth or mental retardation, genital hypoplasia, and ear anomalies and/or deafness) syndrome, diabetic embryopathy, other genetic variants, and FOXN1 deficiency—are associated with congenital athymia.[3]

Patients with congenital athymia are most commonly identified via low or undetectable T-cell receptor excision circles (TRECs) through newborn screening for severe combined immunodeficiency (SCID), which has been required in all 50 states since 2018.[4] The diagnosis is then confirmed using flow cytometry, which identifies profoundly low naive T cells.[1]

Management of patients focuses on supportive care to reduce the risk of infection until the underlying immune deficiency can be corrected.[1] Supportive care includes following reverse isolation protocols in the hospital; isolation and frequent hand washing at home; and prophylaxis to prevent bacterial, fungal, and viral infections as well as monitoring and treatment for infections.[1]

With only supportive care, children with congenital athymia typically do not survive beyond 2 to 3 years of age.[4]



About RETHYMIC[5]

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).

Clinical Studies Design

The safety and efficacy of RETHYMIC was evaluated in 105 patients across 10 prospective, single-center, open-label studies involving a total of 95 patients with pediatric congenital athymia in the primary efficacy analysis.[5]

The primary endpoint of the analysis was the Kaplan-Meier estimated survival at 1 year post-administration of RETHYMIC. Kaplan-Meier estimated survival at 2 years post-treatment was a supportive endpoint. Secondary endpoints included naive and total T-cell numbers and function at 1 year post-treatment. Reductions in the number of infections over time and survival in patients alive at 1 year post-treatment were also analyzed.[3]

Patient Demographics[5]

Characteristic		Primary Efficacy Analysis (N = 95)
Median (range) age at time of treatment, mo		9 (1-36)
Male, %		59
Race, %	White	70
	Black	22
	Asian/Pacific Islander	4
	American Indian/Alaskan Native	2
	Multi-race	2

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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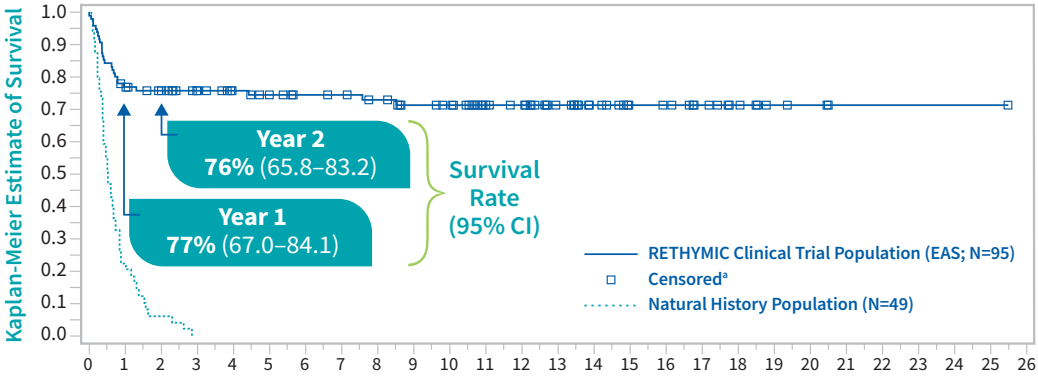
Survival Data[5]

The Kaplan-Meier estimated survival rates at **year 1** and **year 2** were **77%** (95% CI, 0.670-0.841) and **76%** (95% CI, 0.658-0.832), respectively.

Without treatment, congenital athymia is fatal in childhood. In a natural history population observed from 1991 through 2017, 49 patients diagnosed with congenital athymia received supportive care only. The 2-year survival rate was 6%, with all patients dying by 3 years of age.

Kaplan-Meier Survival by Year
(RETHYMIC Efficacy Analysis Population and Natural History Population)



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	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	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.

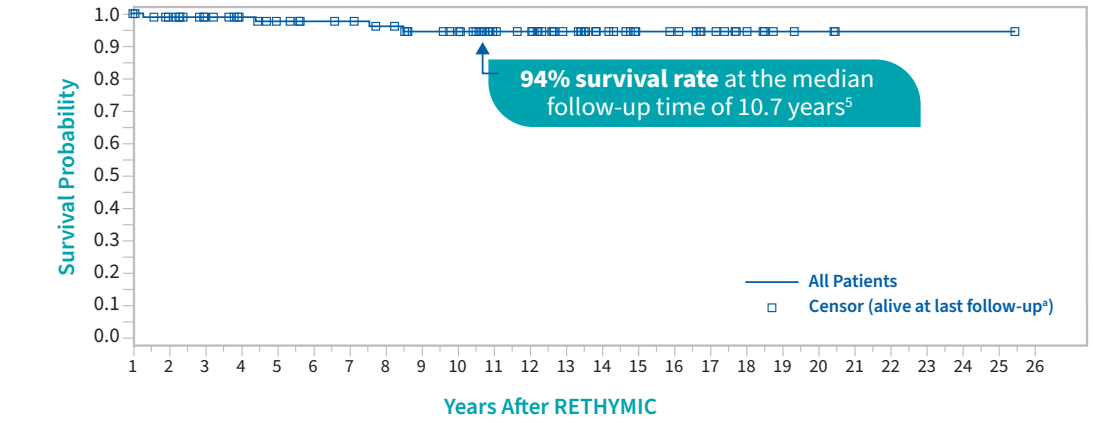
Important Safety Information (cont'd)

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.

Survival Data[3,5] (cont'd)

For patients who were alive at **1 year** after treatment with RETHYMIC, the survival rate was **94%** at a median follow-up of 10.7 years.[5]

Kaplan-Meier Estimated Survival Rate: Follow-up of Patients Who Were Alive 1 Year After RETHYMIC (EAS)[3]



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

[a]Censored patients are alive, and censored at the time of last follow-up.
EAS, efficacy analysis set.

Important Safety Information (cont'd)

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

Please see additional Important Safety Information on pages 14 & 15, and the enclosed full Prescribing Information.

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Immune Reconstitution[5]

Immune reconstitution sufficient to protect from infection is unlikely to develop prior to 6 to 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.

- Naive $CD4^+$ and $CD8^+$ T cells reconstituted over the first year, with a durable increase through year 2
- This was accompanied by functional improvements achieved based on T-cell proliferative responses to the mitogen phytohemagglutinin (PHA)

Development of Naive T Cells Following Treatment With RETHYMIC in the Primary Efficacy Analysis Population[5]

	Baseline	Month 6	Month 12	Month 24
Median naive $CD4^+$ T cells/mm^3	**1.0**	**42**	**212**	**275**
(minimum, maximum)	**(0, 38)**	**(0, 653)**	**(1, 751)**	**(33, 858)**
Number of subjects*	**65**	**67**	**45**	**26**
Median naive $CD8^+$ T cells/mm^3	**0**	**9**	**58**	**86**
(minimum, maximum)	**(0, 46)**	**(0, 163)**	**(0, 304)**	**(6, 275)**
Number of subjects*	**59**	**56**	**40**	**26**

*Enzyvant, Data on File.

Important Safety Information (cont'd)

In the clinical studies of RETHYMIC, 3 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.

Decrease in Infections

RETHYMIC significantly reduced the number of infections over time. In the first year after treatment with RETHYMIC, the number of patients with an infection event onset 6 to ≤12 months after treatment decreased by 38% (from 63 to 39) relative to the number of patients with an infection event onset in the first 6 months post-treatment. A 2-year analysis showed a decrease in both the number of patients with an infection event and the mean number of infection events per patient, with an onset in the first 12 months post-treatment as compared to 12 to ≤24 months after treatment.

2.9 **There was a mean difference of 2.9 events (*P*<0.001) per patient.**

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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Adverse Reactions[5]

The safety data described are derived from 10 prospective, single-center, open-label studies, and include 105 patients who were treated with RETHYMIC and had at least 1 year of follow-up. The following table lists the adverse reactions occurring in 105 patients who were treated with RETHYMIC in these studies.[5]

Adverse Reactions Occurring in at Least 5% of Patients Treated With RETHYMIC During Clinical Studies

System Organ Class Preferred Term	RETHYMIC (N=105) n (%)
Number of Patients With Adverse Reactions[1]	**80 (76)**
Hypertension (high blood pressure)	20 (19)
Cytokine release syndrome[2]	19 (18)
Hypomagnesemia (low magnesium)	17 (16)
Rash[3]	16 (15)
Renal impairment / failure[4] (decrease of kidney function)	13 (12)
Thrombocytopenia[5] (low platelets)	13 (12)
Graft versus host disease[6]	11 (10)
Hemolytic anemia[7] (low red bloods cells)	9 (9)
Neutropenia (low white blood cells)	9 (9)
Respiratory distress[8] (difficulty breathing)	8 (8)
Proteinuria (protein in urine)	7 (7)
Pyrexia (fever)	6 (6)
Acidosis[9]	6 (6)
Diarrhea[10]	5 (5)
Seizure[11]	5 (5)

1. Reactions which occurred in the 2 years after treatment.
2. All events (19/19) of cytokine release syndrome occurred in association with ATG-R treatment.
3. Rash includes rash, granuloma skin, rash popular, urticaria.
4. Renal impairment / failure includes renal failure and acute kidney injury, proteinuria and blood creatinine increased.
5. Thrombocytopenia includes thrombocytopenia and Immune thrombocytopenic purpura.
6. GVHD includes GVHD, GVHD-gut, GVHD-skin, Omenn syndrome.
7. Hemolytic anemia includes autoimmune hemolytic anemia, Coombs-positive hemolytic anemia, hemolysis, hemolytic anemia.
8. Respiratory distress includes respiratory distress, hypoxia, respiratory failure.
9. Acidosis includes acidosis, renal tubular acidosis and blood bicarbonate decreased.
10. Diarrhea includes diarrhea and hemorrhagic diarrhea.
11. Seizures include infantile spasms, seizures and febrile convulsion.

Important Safety Information (cont'd)

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

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.

Adverse Reactions (cont'd)

The most common (>10%) adverse events related to RETHYMIC included hypertension (high blood pressure, 19%), cytokine release syndrome (18%), rash (15%), hypomagnesemia (low magnesium, 16%), renal impairment/failure (decrease of kidney function, 12%), thrombocytopenia (low platelets, 12%), and graft versus host disease (10%).

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

These are not all the side effects that can or may occur with RETHYMIC treatment.

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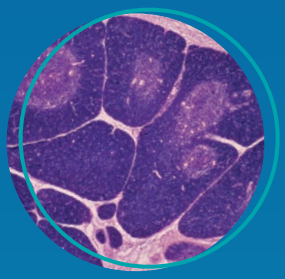
RETHYMIC is engineered human thymus tissue from a living donor



Thymus tissue is obtained from donors ≤9 months of age undergoing cardiac surgery

Not an actual patient

RETHYMIC is then administered in patients with congenital athymia

The science of RETHYMIC[5]

RETHYMIC is human thymus tissue engineered to generate a functioning immune response in pediatric patients with congenital athymia.

The source of the thymus tissue is an infant donor, up to the age of 9 months, undergoing cardiac surgery. Because the thymus sits on top of the heart, some of the infant's thymus tissue needs to be removed to access the heart during surgery. With the consent of the infant donor's parents or guardians, the thymus tissue from pediatric cardiac surgeries is donated for the engineering process to make RETHYMIC.

Processing and Production

RETHYMIC is engineered in a 12- to 21-day process. Unlike a solid organ transplant or some grafts, the RETHYMIC thymus tissue undergoes a manufacturing process to deplete most of the donor thymocytes from the tissue and preserve the thymic epithelial cells and tissue structure.

RETHYMIC is surgically implanted at a single site in Durham, North Carolina.

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.

RETHYMIC Administration and Development of Patient's T Cells[5]

After general anesthesia, a ~5 cm long vertical skin incision is made over the anterior thigh compartment

Individual slices of RETHYMIC are implanted into pockets between muscle fibers*

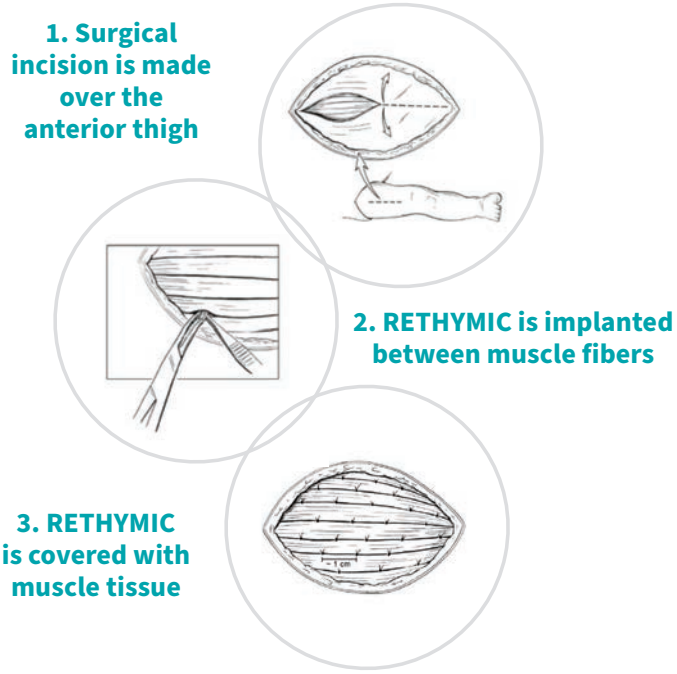
Each implanted RETHYMIC slice is fully covered by muscle tissue and the pockets stitched closed with a single absorbable suture

Following implantation, confirm hemostasis. Close the skin incision with absorbable sutures and apply a standard dressing. Leave the fascia open to allow room for muscle compartment swelling

Subsequently, the patient's own bone marrow stem cells migrate to the implanted RETHYMIC, where they develop into naive, immunocompetent T cells

*Recommended dose range: 5,000 to 22,000 mm^2 of RETHYMIC/m^2 of recipient body surface area.

RETHYMIC is surgically implanted in one (or both, if necessary) of the patient's quadriceps muscles during a single surgical procedure. Implantation of RETHYMIC into the quadriceps requires a healthy bed of muscle tissue.



For patients who respond to RETHYMIC, immune reconstitution sufficient to protect from infection is unlikely to develop prior to 6 to 12 months after treatment with RETHYMIC. Elevated naive T-cell numbers are not observed until 2 years after treatment. Supportive care measures should be continued until immune reconstitution is established.

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.

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Post-treatment care[5]

Proper post-procedure clinical care is critical to support the success of treatment with RETHYMIC.

Strict infection control measures should be observed until the healthcare provider confirms that immune function has been reconstituted through the evaluation of blood using flow cytometry and the criteria for the discontinuation of immunoglobulin replacement therapy and *Pneumocystis jiroveci* pneumonia prophylaxis have been met. Immune reconstitution sufficient to protect from infection is unlikely to develop prior to 6 to 12 months after treatment with RETHYMIC. Elevated naive T-cell numbers are not observed until 2 years after treatment. Supportive care measures should be continued until immune reconstitution is established. Patients and caregivers should follow good handwashing practices, minimize contact with others, and immediately report signs and symptoms of infection to their healthcare provider.

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

Important Safety Information (cont'd)

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.

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Access and support

ENZYVANT CONNECT

Enzyvant CONNECT is a program that helps patients and caregivers by providing personalized support throughout the congenital athymia treatment journey. The Enzyvant CONNECT team can:

- **Provide tools to guide you through each step in the treatment journey**
- **Work with your insurer to help you understand insurance coverage for congenital athymia treatment (Subject to eligibility requirements)**
- **Help you understand what, if any, out-of-pocket costs may be expected**

To enroll your patient, call Enzyvant CONNECT at:
844-ENZCNCT (844-369-2628)
Monday through Friday, 8:00 AM to 8:00 PM ET

Not an actual patient

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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.

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.

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

In the clinical studies of RETHYMIC, 3 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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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.

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

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

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.

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

For more information, please visit RETHYMIC.com

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References

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