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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TREGZI safely and effectively. See full prescribing information for TREGZI.

TREGZI (allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq) suspension, for intravenous infusion
Initial U.S. Approval: 2026

----------INDICATIONS AND USAGE----------
TREGZI™ is an allogeneic regulatory T cell-based immunotherapy with hematopoietic stem and progenitor cells and T cells indicated for use in matched donor hematopoietic stem cell transplantation with myeloablative preparative regimen, for hematopoietic and immunologic reconstitution and to improve chronic graft-versus-host disease (cGVHD)-free survival, in the treatment of adults with hematological malignancies. (1)

----------DOSAGE AND ADMINISTRATION----------
For intravenous use only. (2.1)
- Verify patient's identity prior to infusion. (2.2)
- TREGZI is provided as 4 separate infusion bags (HSPCs, Tregs, Tcons, and Tcon diluent). (2.1)
- Administer an appropriate myeloablative preparative regimen before infusion of TREGZI. (2.2)
- DO NOT use a leukodepleting filter. (2.2)
- See Full Prescribing Information for instructions on receipt, preparation, and administration of TREGZI (2.2, 16)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): TREGZI is a suspension for intravenous infusion. TREGZI is provided in separate infusion bags labeled for the specific patient. A single dose of TREGZI consists of:
- A minimum dose of HSPCs of 1.0×10^6 viable cells per patient kilograms.
- A dose of Tregs of 1.3×10^6 to 3.5×10^6 viable cells per patient kilograms.
- A dose of Tcons of 1.3×10^6 to 6.9×10^6 viable cells per patient kilograms. (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Graft Failure: Monitor patients closely for laboratory evidence of hematopoietic recovery. (5.1)
- Graft-Versus-Host Disease (GVHD): Treat patients with a single agent calcineurin inhibitor as prophylaxis to decrease the risk of GVHD. Monitor for signs and symptoms of GVHD. (5.2)
- Infusion Reactions: Monitor patients for signs and symptoms of infusion reactions during and after TREGZI administration. When a reaction occurs, pause the infusion and institute supportive care as needed. (5.3)
- Secondary Malignancies and Malignancies of Donor Origin: Monitor for secondary malignancies and malignancies of donor origin. (5.4)
- Transmission of Infectious Agents: Monitor patients closely for serious infections. (5.5)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence ≥20%) were mucositis, diarrhea, rash, viral infections, infections-pathogen unspecified, abdominal pain, vomiting, nausea, bacterial infections, hemorrhage, aGVHD, edema, and fungal infections. (6.1)

The most common Grade 3-4 laboratory abnormalities (≥ 20%) are lymphocyte count decreased, platelet count decreased, leukocyte count decreased, neutrophil count decreased, and hemoglobin decreased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Orca Bio at 1-877-290-6722 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised:XX/2026

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TREGZI is indicated for use in matched donor hematopoietic stem cell transplantation with myeloablative preparative regimen, for hematopoietic and immunologic reconstitution and to improve chronic graft-versus-host disease-free survival, in the treatment of adults with hematological malignancies.

2 DOSAGE AND ADMINISTRATION

2.1 Dose

For intravenous use only.

A single dose of TREGZI consists of hematopoetic stem and progenitor cells (HSPCs), regulatory T cells (Tregs), conventional T cells (Tcons), and Tcon diluent provided in 4 separate infusion bags labeled for the specific patient. Each patient-specific infusion bag of TREGZI contains a batch-dependent concentration of allogeneic cells (see Table 1). Patient-specific dose information can be found within the Certificate of Analysis (COA).

Table 1 TREGZI Route of Administration, Dose Regimen, and Target Dose Range

Component	Dose Regimen	Target Viable Cell Dose Range (Cells per Patient kg)
HSPCs	Intravenous, once, on day 0	≥1.0×10^6
Tregs	Intravenous, once, on day 0 immediately after administration of HSPCs	1.3×10^6 to 3.5×10^6
Tcons	Intravenous, once, on day +2 to +3 (after the start of HSPC infusion on day 0)	1.3×10^6 to 6.9×10^6
Tcon diluent	Intravenous, once, administered with Tcons drug product on day +2 to +3 (after HSPC infusion on day 0)	30 mL

Abbreviations: HSPCs, hematopoietic stem and progenitor cells; Tregs, regulatory T cells; Tcons, conventional T cells.

2.2 Preparation and Administration

Preparing Patient for TREGZI Infusion

Pretreatment

- Administer an appropriate myeloablative preparative regimen before infusion of TREGZI.

Receipt of TREGZI

Do not irradiate.

TREGZI is shipped directly to the treatment center in two transport containers *[See How Supplied/Storage and Handling (16)]*:

- A refrigerated cardboard shipping container at 2ºC to 8ºC (36°F to 46°F), containing the HSPC infusion bag and Treg infusion bag in a single protective carton.
- A cardboard box containing:
    1) A liquid nitrogen dry vapor shipper at below -125ºC (below -193°F), containing the cryopreserved Tcon infusion bag in a protective metal cassette.
    2) A protective carton containing the Tcon diluent infusion bag stored at ambient temperature (20ºC to 25ºC, 68ºF to 77ºF).

Upon receipt of the refrigerated cardboard shipping container containing the HSPC and Treg carton and infusion bags:

- Match the identity of the patient with the patient identifiers on the carton and infusion bags containing the HSPCs and Tregs. If the information on the patient-specific label does not match the intended patient, do NOT infuse TREGZI and contact Orca Bio at 1-877-411-6722.
- Inspect the HSPC and Treg infusion bags for any breaches of bag integrity such as breaks, leaking by the port line seal, or cracks. If an infusion bag is compromised, follow the institutional procedures for handling, storage and disposal and contact Orca Bio at 1-877-411-6722.

Upon receipt of the cardboard box containing the (1) Tcon metal cassette and infusion bag and (2) Tcon diluent carton and infusion bag:

- Do NOT open the Tcon metal cassette upon receipt. Only open the metal cassette to verify the patient identifiers and inspect the Tcon infusion bag immediately prior to thawing.
- Match the identity of the patient with the patient identifiers on the (1) metal cassette containing the Tcon infusion bag and (2) carton and infusion bags containing the Tcon diluent. If the information on the patient-specific label does not match the intended patient, do NOT infuse TREGZI and contact Orca Bio at 1-877-411-6722.
- Inspect the Tcon diluent infusion bag for any breaches of bag integrity such as breaks, leaking by the port line seal, or cracks. If an infusion bag is compromised, follow the institutional procedures for handling, storage and disposal and contact Orca Bio at 1-877-411-6722.

Premedication

- Administer diphenhydramine and/or acetaminophen approximately 30 minutes before TREGZI HSPC and Tcon infusions per institutional guidance.
- The use of corticosteroids as premedication is strongly discouraged.

Day 0: Preparation and Administration of TREGZI HSPCs and Tregs

- Confirm the patient's identity matches the patient identifiers on each of the HSPC and Treg infusion bags. Do NOT infuse the HSPCs and Tregs if the information on the patient-specific label does not match the intended patient.
- Central venous catheter access is recommended for TREGZI infusion.
- Infuse HSPCs (Step 1 of Administration) and Tregs (Step 2 of Administration) promptly after receipt and verification of the expiry date and time listed on the bag label, carton label or Certificate of Analysis (COA).
- Infuse HSPCs and Tregs immediately after removal from refrigeration. Do not warm infusion bags prior to infusion.

Day 0: Preparation of HSPCs and Tregs for Infusion

1. Remove the HSPC and Treg infusion bags from refrigerated storage immediately prior to infusion.
2. Agitate each infusion bag by inverting or gently massaging to prevent cell clumping. If visible cell clumping remains, continue to disperse clumps per institutional guidance prior to infusion.

Day 0: Administration of HSPCs and Tregs

Do NOT use a leukodepleting filter.

3. Prime the tubing with 0.9% sodium chloride.
4. Infuse the entire contents of HSPC infusion bag (Step 1 of Administration) by either gravity or a peristaltic pump at a rate of up to 5 mL/min.
5. After infusion of the entire contents of the HSPC infusion bag, add approximately 10 mL of 0.9% sodium chloride to the empty infusion bag and administer to the patient at the same infusion rate per institutional guidance. Repeat this process to achieve a total of two rinses.
6. Immediately after infusion of the HSPCs and two rinses on day 0, infuse the entire contents of the Treg infusion bag by either gravity or a peristaltic pump at a rate of up to 5 mL/min.
7. After infusion of the entire contents of the Treg infusion bag, add approximately 10 mL of 0.9% sodium chloride to the empty infusion bag and administer to the patient at the same infusion rate per institutional guidance. Repeat this process to achieve a total of two rinses.

Day +2 to Day +3: Preparation and Administration of TREGZI Tcons

- Tcons are supplied cryopreserved in an infusion bag that is protected by a corresponding overwrap bag and packed in a metal cassette. Patient identifiers are found on the cassette and infusion bag labels. Do NOT open the metal cassette until immediately before thawing.
- Confirm the patient's identity matches the patient identifiers on the Tcon and Tcon diluent infusion bags. Do NOT infuse the Tcons if the information on the patient-specific label does not match the intended patient.

- Central venous catheter access is recommended for TREGZI infusion.
- Infuse Tcons (Step 3a of Administration) after thaw and dilution using the Tcon diluent (Step 3b of Administration) as soon as possible. If the Tcons can not be administered immediately, the Tcon infusion bag must be stored at 2°C to 8°C and infused within 4 hours.

Day +2 to Day +3: Preparation - Thawing of Tcons

Preparation of the Tcons for infusion occurs on day +2 to +3 after the start of HSPC infusion on day 0.

1. Refrigerate the Tcon diluent infusion bag at 2°C to 8°C for at least 30 minutes prior to removing the Tcon metal cassette from liquid nitrogen storage.
2. Remove Tcon metal cassette from liquid nitrogen storage.
3. Open the protective cassette and remove the Tcon infusion bag. Remove the Tcon infusion bag from the overwrap bag.
4. Place Tcon infusion bag in a sterile plastic bag and seal the bag tightly.
5. Place the sealed plastic bag in a 37°C water bath for approximately 1 to 1.5 minutes until the cell suspension is slushy in texture. Gently massage the Tcon infusion bag during thawing.
6. Remove the sealed bag from the water bath and remove the Tcon infusion bag.
7. Discard outer plastic bag.
8. Wipe down the Tcon infusion bag with 70% isopropanol.

Day +2 to Day +3: Preparation - Dilution of Tcons with Tcon Diluent

9. Remove the Tcon diluent infusion bag from refrigeration.
10. Using a dispensing pin and syringe or transfer set with gravity, over a period of 3 minutes, slowly transfer the contents of the Tcon diluent infusion bag into the Tcon infusion bag. Rock the infusion bag back and forth during transfer to mix.
11. If administering the Tcons immediately, store the Tcon infusion bag at room temperature (18ºC to 25ºC). If not administering the Tcons immediately, store the Tcon infusion bag at 2°C to 8°C.
12. Immediately prior to infusion, gently agitate each infusion bag by inverting or gently massaging to prevent cell clumping per institutional guidance. If visible cell clumping remain continue to disperse clumps by gentle massaging per institutional guidance prior to infusion.

Day +2 to Day +3: Administration of Tcons

DO NOT use a leukodepleting filter.

13. Prime the tubing with 0.9% sodium chloride.
14. Infuse the entire contents of the Tcon infusion bag by either gravity or a peristaltic pump at a rate of up to 5 mL/min.
15. After infusion of the entire contents of Tcon infusion bag, add approximately 10 mL of 0.9% sodium chloride to the empty infusion bag and administer to the patient at the same infusion rate per institutional guidance. Repeat this process to achieve a total of two rinses.

16. Treat patients with a single agent calcineurin inhibitor as prophylaxis to decrease the risk of GVHD starting the day after Tcon administration.

TREGZI contains human blood cells. Follow universal precautions and local biosafety guidelines for handling and disposal to avoid potential transmission of infectious diseases.

3 DOSAGE FORMS AND STRENGTHS

TREGZI is a cell suspension for intravenous infusion. TREGZI is provided in separate infusion bags labeled for the specific patient. Each single-dose, patient-specific infusion bag of TREGZI contains a batch-dependent concentration of allogeneic cells as described in Table 2. Patient-specific dose information can be found within the COA.

Table 2 TREGZI Cell Components and Diluent

Cell Component	**Target Viable Cell Dose Range (Cells per Patient kg)**	**Excipients**	**Appearance**	**Container and Approximate Fill Volume**	**Component Identifying Information**
HSPCs	≥1.0×10^6	MEI, Type 1 HSA	Clear to opaque liquid Color = off-white, white, yellow, orange, to red	Fill volume: approximately 100 mL	Orange colored label specifying “Step 1 of Administration”
Tregs	1.3×10^6 to 3.5×10^6	MEI, Type 1 HSA	Clear to opaque liquid Color = off-white, white, yellow, orange, to red	Fill volume: approximately 100 mL	Light blue colored label specifying “Step 2 of Administration”
Tcons	1.3×10^6 to 6.9×10^6	MEI, Type 1, HSA, DMSO Hetastarch (6% hetastarch in 0.9% sodium chloride injection added at 30.5% (v/v)).	Clear to opaque liquid Color = off-white, white, yellow, orange, to red	Fill volume: approximately 15 mL	Dark blue colored label specifying “Step 3a of Administration”
Diluent					
Tcon Diluent	Not Applicable	MEI Type 1, HSA	Clear Color: Colorless to yellow	Fill volume: approximately 38 mL	Tan label specifying “Step 3b of Administration”

Abbreviations: DMSO, dimethyl sulfoxide; HSA, human serum albumin; HSPCs, hematopoietic stem and progenitor cells; MEI, multiple electrolytes injection; Tcons, conventional T cells; Tregs, regulatory T cells.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Graft Failure

Graft failure has occurred after TREGZI administration *[see Adverse Reactions (6.1)]*. Screen TREGZI recipients for antidonor antibodies that may prevent engraftment. Monitor patients closely for laboratory evidence of hematopoietic recovery.

5.2 Graft-Versus-Host Disease

Acute and chronic Graft-Versus-Host disease (GVHD), including life-threatening and fatal cases, occurred following treatment with TREGZI *[see Adverse Reactions (6.1)]*. Acute GVHD manifests as maculopapular rash, gastrointestinal symptoms, and elevated bilirubin. Chronic GVHD may include skin rash, mouth sores, dry eyes, liver inflammation, and development of scar tissue in the skin and joints and damage to the lungs. Treat patients with a single agent calcineurin inhibitor as prophylaxis to decrease the risk of GVHD. Monitor for signs and symptoms of GVHD, and treat if GVHD develops.

5.3 Infusion Reactions

Infusion reactions (IRs) may occur during or following treatment with TREGZI. Serious hypersensitivity reactions including anaphylaxis may occur due to DMSO, human serum albumin (HSA), Dextran or murine protein present in TREGZI. IRs may begin within minutes of the start of TREGZI infusion, although symptoms may continue to intensify and not peak for several hours after the completion of the infusion. Monitor patients for signs and symptoms of IRs during and after TREGZI administration. When a reaction occurs, pause the infusion and institute supportive care as needed. Premedicate patients with antipyretics and histamine antagonists prior to infusion to reduce the incidence and intensity of infusion reactions.

5.4 Secondary Malignancies and Malignancies of Donor Origin

Secondary malignancies and malignancies of donor origin may occur following treatment with TREGZI *[see Adverse Reactions (6.1)]*. Development of secondary malignancies, including posttransplantation lymphoproliferative disorder (PTLD) may occur many years after transplantation. PTLD manifests as a lymphoma-like disease favoring non-nodal sites. PTLD is usually fatal if not treated. Serial monitoring of blood for EBV DNA may be warranted in patients with persistent cytopenias. No patient treated with TREGZI has developed PTLD. Monitor for malignancies of donor origin and secondary malignancies.

Contact Orca Bio at 1-877-411-6722 if any patient is diagnosed with a secondary malignancy or a malignancy of donor origin.

5.5 Transmission of Infectious Agents

Transmission of serious infectious or communicable disease or agents may occur with TREGZI treatment as it is derived from human donor blood and manufactured using animal-derived reagents. Risks of transmission of infectious agents may occur despite screening or testing of donors. Risks of transmission of serious infections include, but are not limited to, human immunodeficiency virus, human T cell lymphotropic virus (HTLV)-1 and -2, hepatitis B virus (HBV), hepatitis C virus (HCV),

Treponema pallidum, Trypanosoma cruzi, West Nile virus (WNV), cytomegalovirus, transmissible spongiform encephalopathy agents and vaccinia. Monitor patients for signs and symptoms of infections, perform tests for infectious agents and treat as clinically indicated.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described in this section reflects exposure to TREGZI in one clinical study (Precision-T Study) which enrolled patients with advanced hematologic malignancies eligible for HLA-matched allogeneic stem cell transplantation following myeloablative preparative regimen. The study treated 88 patients with TREGZI and 94 patients with standard of care (SoC) unmanipulated graft. The patients were followed for a duration of 24 months *[see Clinical Studies (14)].*

Serious adverse reactions within the first 100 days occurred in 25 patients (28%) treated with TREGZI including bacterial infections (n=12; 14%), pyrexia (n=4; 5%), venooclusive liver disease (n=3; 3%), and viral infections (n=3; 3%) and venooclusive liver disease (n=3; 3%). Fatal adverse reactions occurred in 3 patients (3%).

Non-relapse deaths at 12 months occurred in 3/88 (3.4%) patients in the TREGZI group and in 11/94 (11.7%) patients in the SoC control group *[see Clinical Studies (14)].*

In the TREGZI treated safety population, the most common (greater than or equal to 10%) Grade 3 or 4 nonlaboratory adverse reactions were mucositis (28%), bacterial infection (18%), infection – pathogen unspecified (18%), and viral infection (14%).

Table 3 summarizes the most common nonlaboratory adverse reactions occurring in ≥10% patients treated with TREGZI or unmanipulated allograft control group in Precision-T Study.

Table 3 Adverse Reactions occurring in ≥10% of patients treated with TREGZI or unmanipulated allograft control arm in Precision-T Study

Adverse Reactions	TREGZI (N = 88)		SoC Control (N=94)	
	All Grades %	Grade 3 or Higher %	All Grades %	Grade 3 or Higher %
Infections and infestations[a]				
Viral infections	51	14	47	19
Infections - pathogen unspecified	45	18	56	30
Bacterial infections	40	18	38	16
Fungal infections	20	3	18	0
Gastrointestinal disorders				
Diarrhea*	69	1	79	6
Abdominal pain*	45	0	54	1
Vomiting	44	1	35	0
Nausea*	41	1	44	2
Immune system disorders				
Acute graft-versus-host disease[b]	38	6	46	15
General disorders and administration site conditions				
Mucositis*	85	28	88	37
Edema*	30	0	38	3
Respiratory, thoracic and mediastinal disorders				
Pneumonia	5	5	17	15
Skin and Subcutaneous Tissue Disorders				
Rash*	65	0	55	0
Vascular Disorders				
Hemorrhage*	39	6	33	1

Abbreviations: GVHD, Graft-Versus-Host disease.
* includes multiple related terms
[a] Infections and infestations were calculated for the first 2 years after transplantation.
[b] Acute GVHD graded by MAGIC standardization criteria (Harris 2016) as determined by an independent review committee; calculated for the first year after transplantation.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with TREGZI include the following:

- *Hepatobiliary disorders:* veno-occlusive liver disease 3% in TREGZI group and 2% in control group.
- *Immune system disorders:* moderate to severe chronic Graft-versus-host disease (GVHD) 13% in TREGZI group and 41% in control group as per International NIH Chronic GVHD Diagnosis and Staging.
- *Injury, poisoning, and procedural complications:* Secondary graft failure 1% in TREGZI group and 0% in control group.

Table 4 summarizes the most common Grade 3 or 4 laboratory abnormalities occurring in ≥10% of patients in Precision-T Study.

Laboratory Abnormalities

Table 4 Grade 3 or 4 Laboratory Abnormalities Occuring in ≥10% of Patients in Precision-T Study

Laboratory Abnormality[a,b]	TREGZI Grade 3 or 4 %	SoC Control Grade 3 or 4 %
Lymphocyte count decereased	98	94
Platelet count decreased	93	96
Leukocyte count decreased	89	89
Neutrophil count decreased	77	83
Hemoglobin decreased	71	81
Alanine aminotransferase increased	12	7

[a] Includes lab abnormalities for the first 100 days
[b] Baseline lab values were assessed prior to conditioning regimen. Denominators ranged from 79 to 87 for TREGZI arm and 90 to 93 for Control arm for lab tests, based on the number of patients with a baseline value and at least one post treatment value for each lab test.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are no available data on TREGZI use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with TREGZI to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if TREGZI has the potential to be transferred to the fetus. TREGZI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Report all pregnancies following treatment with TREGZI to Orca Bio at 1-877-411-6722.

In the United States (U.S.) general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary
There are no available data on the presence of TREGZI in human milk, the effect on the breastfed infant, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TREGZI and any potential adverse effects on the breastfed infant from TREGZI or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing
Females of reproductive potential should have a pregnancy test prior to starting the conditioning regimen for TREGZI.

Contraception
There are insufficient exposure data to provide a recommendation concerning the duration of contraception following treatment with TREGZI. See the prescribing information of selected myeloablative regimens for reccomendations on use of contraception.

Infertility
There are no data on the effect of TREGZI on fertility.

8.4 Pediatric Use

Safety and efficacy of TREGZI in pediatric patients have not been established.

8.5 Geriatric Use

Although Precision-T Study did not include any patients aged 65 years and older, some patients over 65 years of age participated in other TREGZI studies using a myeloablative or reduced intensity conditioning (RIC) regimen. However, the number of patients was inadequate to allow subgroup analysis to support recommendations in the geriatric population.

11 DESCRIPTION

TREGZI (allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq) is an allogeneic hematopoietic stem cell and T-cell immunotherapy isolated from the mobilized peripheral blood of an 8/8 HLA-matched related or unrelated donor and is donor- and recipient-specific.

TREGZI is composed of individual cell suspensions for intravenous infusion of 1) purified hematopoietic stem and progenitor cells (HSPCs), 2) regulatory T cells (Tregs), and 3) conventional T cells (Tcons). In addition, 4) a chemically defined diluent is provided to dilute the Tcons before infusion.

1. HSPCs (CD34+ cells) are formulated in approximately 100 mL of Multiple Electrolytes Injection (MEI), Type 1 and 2% (w/v) human serum albumin (HSA) and filled into an infusion bag. In addition to the HSPCs cells, other cell populations present may include lymphocytes, erythrocytes, and platelets. The HSPCs contain less than 50 x 10^3 T cells per kg. The cell suspension appears off-white, white, yellow, orange, to red in color. The HSPC infusion bag is supplied in a carton with the Treg infusion bag.
2. Tregs (CD4+CD25+CD127-/low cells) are formulated in approximately 100 mL of MEI, Type 1 and 2% (w/v) HSA and filled into an infusion bag. In addition to the Tregs, other cell populations present may include T cells, NK cells, B cells, monocytes, granulocytes, and erythrocytes. The cell suspension appears off-white, white, yellow, orange, to red in color. The HSPC infusion bag is supplied in a carton with the Treg infusion bag.
3. Tcons (CD3+ cells) are formulated in approximately 15 mL of MEI, 3% to 4% (w/v) HSA, 7.5% DMSO, and Hetastarch (6% hetastarch in 0.9% sodium chloride injection added at 30.5%

(v/v)), filled into an infusion bag, cryopreserved in a protective metal cassette. In addition to T cells, other cell populations present may include HSPCs, erythrocytes, and other lymphocytes. The cell suspension appears off-white, white, yellow, orange, to red in color.

4. The Tcon diluent contains approximately 38 mL of MEI and 2% (w/v) HSA and is filled into an infusion bag. The Tcon diluent appears colorless to yellow. The Tcon diluent is completely transferred to the Tcon infusion bag prior to Tcon infusion *[see Dosage and Administration (2.3)]*.

The HSPC, Treg and Tcon suspensions must pass a rapid microbial detection test prior to administration. Complete sterility test results are available approximately 14-days post-administration. The Tcon diluent must pass a sterility test before release for shipment.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TREGZI is isolated from the mobilized peripheral blood of a donor HLA-matched to the recipient, and administered after appropriate cytoreductive conditioning. TREGZI contains purified regulatory T cells (Tregs) and conventional T cells (Tcons). The exact mechanism by which Tregs exert their effects is not fully understood. Tregs are administered prior to Tcons to control GVHD and promote immune reconstitution. Nonclinical studies have shown that Tregs suppress Tcon activation and proliferation in secondary lymphoid organs and GVHD target organs, and improve immune reconstitution without compromising graft-versus-tumor (GVT) effects of Tcons. The immunosuppressive activity of Tregs occurs through various immunoregulatory mechanisms, which help preserve immune function and decrease severity of GVHD. Tcons are administered approximately two days later to accelerate immune reconstitution, characterized by the complete or partial restoration of peripheral blood T-cell counts. Immune reconstitution is thought to result in graft-versus-infection and graft-versus-leukemia effects.

TREGZI also contains allogeneic hematopoietic stem and progenitor cells (HSPCs). HSPCs home to the bone marrow, engraft, self-renew, proliferate, and differentiate into all mature blood cells. The mature cells are released from the bone marrow, circulate in the blood stream, and migrate to tissue sites, restoring blood counts and hematopoetic function.

12.2 Pharmacodynamics

No studies have been conducted to evaluate the pharmacodynamics of TREGZI.

12.3 Pharmacokinetics

No studies have been conducted to evaluate the pharmacokinetics of TREGZI.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No nonclinical studies were performed to evaluate the effect of TREGZI on carcinogenesis, mutagenesis, or impairment of fertility.

14 CLINICAL STUDIES

The efficacy of TREGZI was evaluated in a multicenter, open-label, randomized, controlled study (Phase 3 Precision-T Study; NCT05316701). The study enrolled adult patients with 1) acute leukemias (acute lymphoblastic leukemia [ALL], acute myelogenous leukemia [AML], or mixed phenotype/ undifferentiated) in complete remission (CR) or CR with incomplete recovery (CRi) or 2) myelodysplastic syndrome (MDS): i) with ≤10% blast burden in the bone marrow and who were eligible for allogeneic transplant per 2017 International Expert Panel recommendations[1] including high-risk IPSS-R≥5, or poor risk genetic features, or failed nontransplant therapies including erythropoietin-stimulating agents (ESAs), lenalidomide, hypomethylating agents (HMAs), or intensive chemotherapies or ii) therapy-related/secondary MDS as defined by the World Health Organizaton (WHO) classification of myeloid malignancies. Patients with prior history of allogeneic hematopoietic stem cell transplantation were excluded.

In total, 187 patients were randomized to receive either TREGZI (n=93) in the treatment group or an unmanipulated allograft in the control group (n=94). Of the 93 patients randomized to the TREGZI, 88 patients were treated with TREGZI. The reasons for not receiving TREGZI were as follows: One patient received cryopreserved SoC alloHCT because of COVID, 2 patients withdrew consent prior to treatment, 1 patient relapsed and did not enter remission, and 1 patient received TREGZI after the data cutoff date. The median (min, max) time from randomization to transplant is 9 days (6, 26) for patients who received TREGZI (N=88) and 8 days (6, 24) for patients who received SoC (N=94). Both TREGZI and the unmanipulated allograft were derived from G-CSF-mobilized peripheral blood apheresis product from 8/8 (at alleles A, B, C, and DRB1) HLA-matched sibling donors (MSD) or unrelated donors (MUD) and were administered after a myeloablative preparative regimen such as total body irradiation (TBI)-based or chemotherapy-based options. Patients in the TREGZI group received HSPC and Treg components on Day 0, Tcon component on Day 2 or 3 (if no evidence of uncontrolled bacterial, viral, or fungal infection and Karnofsky performance score ≥30%) and tacrolimus within 12 hours after T con infusion as GVHD prophylaxis. Patients in the control group received unmanipulated allograft on Day 0 and tacrolimus starting on Day-3 and methotrexate starting on Day 1 as GVHD prophylaxis.

The population demographics and characteristics were as follows: The median age was 44 years (range: 19 to 65 years), 103 patients (55%) were male, 139 patients (74%) were white, 18 patients (10%) were Asian, 3 patients (2%) were black, 3 patients (2%) American Indian or Alaskan Native, 2 patients (1%) were Native Hawaiian or Other Pacific Islander, and 22 patients (12%) had race not reported. The primary disease diagnoses were as follows: 57 patients (31%) with ALL, 100 patients (54%) with AML, 23 patients (12%) with MDS, and 7 patients (4%) with mixed phenotype acute luekemia (MPAL). Patients received the following myeloablative preparative regimen: 58 patients (31%) received TBI-based conditioning regimens, 126 (67%) received Busulfan-Fluradabine-Thiotepa conditioning regimens, 3 patients (2%) did not receive any conditioning regimen and treatment. DRI score was high in 36 patients (19%) and intermediate in 151 patients (81%). Baseline HCT-CI score were as follows: 45 patients (24%) were with score 0, 90 patients (48%) were with score 1-2, and 52 patients (28%) were with score 3-5. Ninety-five patients (51%) received a graft from 8/8 HLA matched sibling and 92 patients (49%) received a graft from 8/8 HLA matched unrelated donor. The demographics, disease characteristics, conditioning regimens, DRI score, HCT-CI score, and graft source were balanced between TREGZI group and the control group.

The primary efficacy endpoint was cGVHD-free survival (cGFS), defined as the time from HCT to death by any cause or moderate to severe cGVHD, as graded per National Institutes of Health [NIH]

consensus criteria and determined by an independent review committee. To control the Type I error rate, other efficacy endpoints were tested in the following hierarchical order: time to moderate/severe chronic GVHD (cGVHD), overall survival (OS), and GVHD-free/relapse-free survival (GRFS).

The study demonstrated a statistically significant improvement in cGFS and time to moderate/severe cGVHD in patients randomized to TREGZI compared with patients randomized to control. Table 5 and Figure 1 below summarize the efficacy results from Precision-T Study.

Table 5 Efficacy Results from Precision-T Study

Endpoint	TREGZI (N = 93)[3]	SoC Control (N = 94)	Comparison
cGFS[a]			
Number (%) of patients with events	14 (15.1%)	44 (46.8%)	
Median, months [95% CI]	NE [NE, NE]	7.3 [6.3, 15.5]	
P value (log-rank)			<.00001
Hazard Ratio[1] [95% CI]			0.26 [0.14, 0.47]
Time to moderate or severe cGVHD[b]			
Number (%) of patients with events	7 (7.5%)	30 (31.9%)	
Cumulative Incidence % at 12 months [95% CI]	12.6 [5.3, 23.1]	44.0 [31.3, 56.1]	
P value (Gray's test)			.00002
Hazard Ratio[2] [95% CI]			0.19 [0.08, 0.43]

Abbreviations: cGFS, cGVHD-free survival; cGVHD, chronic graft-versus-host disease; CI, confidence interval; DRI, Disease Risk Index; EAC, endpoint adjudication committee, HLA, human leukocyte antigen; MSD, matched sibling donor; MUD, matched unrelated donor; NE, not estimable. NIH, National Institutes of Health; SoC, standard of care.

[a] Stratified log-rank test was used to compare cGFS per EAC between the TREGZI group and the control group

[b] Stratified Gray's test was used to compare time to moderate or severe cGVHD per EAC between the TREGZI group and the control group, treating death as a competing risk. An event for this time-to-event endpoint was defined as the first occurrence of moderate to severe cGVHD per NIH consensus criteria. Patients were followed for cGVHD for 2 years post transplant.

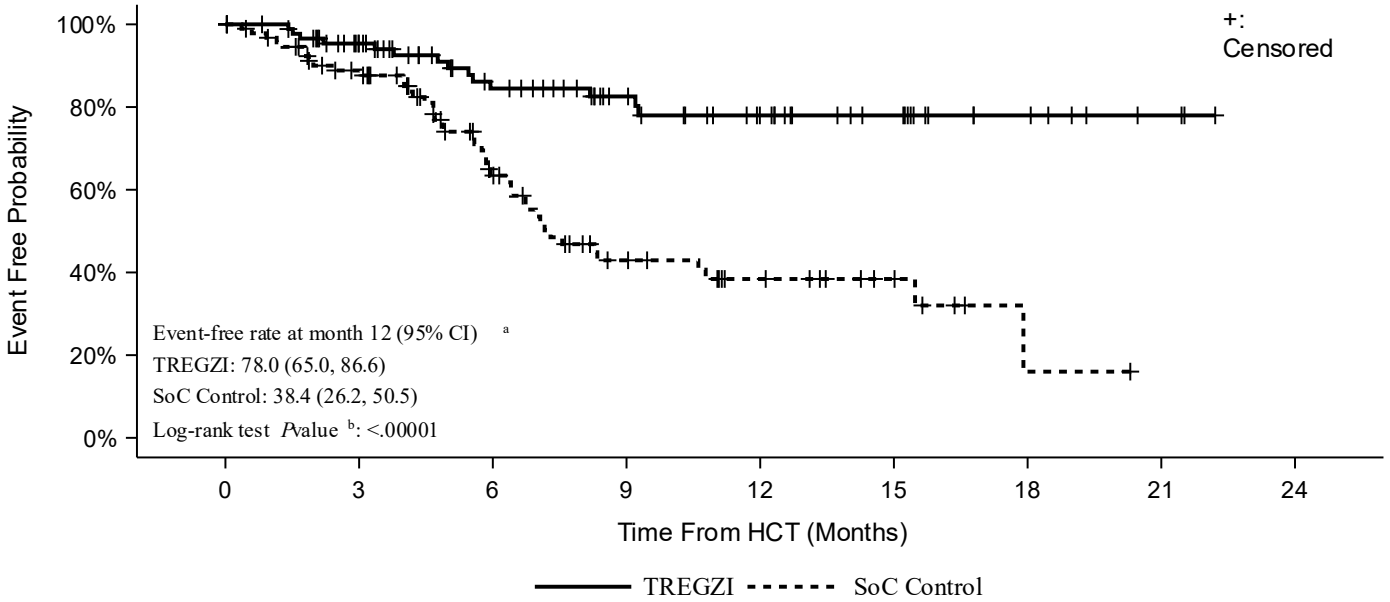
[1] Based on a stratified Cox proportional hazards model

[2] Based on a stratified subdistribution proportional hazards model

[a,b,1,2] Stratified by randomization stratification factors: donor type (8/8 HLA-MSD versus 8/8 HLA-MUD) and DRI risk category (intermediate risk versus high risk)

[3] Four subjects randomized to the TREGZI group did not receive treatment and were censored at Day 1. One subject randomized to the TREGZI group received cryopreserved SoC alloHCT and was analyzed according to the randomized treatment assignment.

Figure 1: Kaplan-Meier Curve of cGFS in Precision-T Phase 3 (Intention-to-Treat Analysis Set)



At risk (Events)									
TREGZI	93 (0)	72 (4)	51 (11)	37 (12)	26 (14)	17 (14)	8 (14)	3 (14)	0 (14)
SoC Control	94 (0)	74 (10)	41 (28)	21 (40)	13 (42)	7 (42)	1 (44)	0 (44)	

The median duration of follow up was 8.48 (range: 0 to 22.2) months on the TREGZI arm and 9.03 (range: 0 to 20.3) months on the control arm.

At 12 months, the Kaplan-Meier estimate of cGFS was 78.0% (95% CI: 65.0%, 86.6%) for TREGZI compared with 38.4% (95% CI: 26.2%, 50.5%) for the control group.

Seven patients (7.5%) in the TREGZI group and 15 patients (16.0%) in the control group died on study with a median follow-up for survival of 11.04 (range: 0.2 to 23.9) months and 11.47 (range: 0.7 to 24.3) months, respectively.

Fifteen patients (16.1%) in the TREGZI group and 10 patients (10.6%) in the control group relapsed on study.

All 88 patients (100%) treated with TREGZI achieved a neutrophil count of 500/mm^3 within 28 days of infusion. Of these, 53 patients (60.2%) had neutrophil counts greater than 500/mm^3 on three consecutive days, confirming neutrophil recovery within 28 days of infusion.

Myeloid-lineage donor chimerism data were available for 68 of 88 patients treated with TREGZI. Among these 68 patients, all demonstrated myeloid-lineage donor chimerism >95% at Day +28 post-transplant.

15 References

1 de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. Blood. 2017;129(13):1753-1762. doi:10.1182/blood-2016-06-724500

16 HOW SUPPLIED/STORAGE AND HANDLING

TREGZI (NDC-85866-223-04) is provided as a single dose and intended for use by a single patient.

TREGZI is provided in two transport containers:

- A refrigerated shipping container at 2°C to 8°C (36°F to 46°F), containing the HSPC infusion bag (NDC 85866-124-01) and Treg infusion bag (NDC 85866-125-01) in a single protective carton (NDC 85866-123-02).
- A cardboard box containing:
    1) A liquid nitrogen dry vapor shipper at below -125°C (below -193°F) , containing the cryopreserved Tcon infusion bag (NDC 85866-126-01) in a protective metal cassette (NDC 85866-126-02). The prescribing information is also included in the shipper.
    2) A protective carton (NDC 85866-127-02) at ambient temperature (20ºC to 25ºC, 68ºF to 77ºF) containing the Tcon diluent infusion bag (NDC 85866-127-01).

Table 6 TREGZI National Drug Codes (NDCs)

Bag (Container) and Carton (Package) Name	**NDC**
TREGZI (all components, located on Certificate of Analysis)	NDC 85866-223-04
HSPC Infusion Bag Label	NDC 85866-124-01
Treg Infusion Bag Label	NDC 85866-125-01
Tcon Infusion Bag Label	NDC 85866-126-01
Tcon Diluent Infusion Bag Label	NDC 85866-127-01
Carton for Treg and HSPC	NDC 85866-123-02
Cassette Label for Tcon	NDC 85866-126-02
Carton for Tcon Diluent	NDC 85866-127-02

Refrigerated TREGZI HSPCs and Tregs

The HSPCs and Tregs are shipped at 2°C to 8°C (36°F to 46°F). The HSPCs and Tregs are in separate infusion bags labeled for a specific patient. The HSPC and Treg infusion bags are provided together in one protective carton, also labeled for a specific patient.

- The HSPCs are provided ready-to-infuse in an 150 mL infusion bag with an orange-colored label specifying “Step 1 of Administration” (NDC 85866-124-01).
- The Tregs are provided ready-to-infuse in an 150 mL infusion bag with a light blue-colored label specifying “Step 2 of Administration” (NDC 85866-125-01).
- Match the identity of the patient with the patient-specific identifiers on the infusion bag and carton labels upon receipt.
- Store the Tregs and HSPCs in refrigerated storage at 2°C to 8°C (36°F to 46°F) until the time of use *[see Dosage and Administration (2.2)]*. Per institutional guidelines, Tregs and HSPCs may be kept in shipping container or moved to refrigerated storage up to the expiry time.

- Do not freeze.

Cryopreserved TREGZI Tcons

The Tcons are shipped frozen in vapor phase of liquid nitrogen at below -125°C (below -193°F). The Tcon infusion bag is contained in an overwrap bag packed in a protective metal cassette. Both the Tcon infusion bag and cassette are labeled for a specific patient. The infusion bag label can not be observed when packaged in the protective metal cassette.

Do NOT open the Tcon metal cassette upon receipt. Only open the metal cassette immediately prior to thawing.

- The Tcons are provided in a 50 mL infusion bag with a dark blue-colored label specifying “Step 3a of Administration” (NDC 85866-126-01).
- The Tcons must be thawed and diluted with the Tcon diluent prior to infusion *(see Preparation and Administration (2.2)]*.
- Match the identity of the patient with the patient-specific identifiers on the cassette label upon receipt. Do NOT open the cassette.
- Store the frozen Tcons in the vapor phase of liquid nitrogen (below -125ºC (below -193°F)) in a temperature-controlled system or in the provided dry shipper.
- The Tcon label includes an expiry date and time corresponding to 7 days from the time of completion of the first apheresis collection used to manufacture the product.
- Immediately prior to thawing, open the cassette and match the identity of the patient with the patient-specific identifiers on the infusion bag.
- Once thawed and diluted, Tcons should be administered as soon as possible but within 4 hours when stored at 2°C to 8°C (36°F to 46°F).

TREGZI Tcon diluent

The Tcon diluent is shipped at ambient temperature (20ºC to 25ºC, 68ºF to 77ºF). The Tcon diluent infusion bag is packaged in a protective carton. Both the infusion bag and carton are labeled for a specific patient.

Do NOT directly infuse the Tcon diluent into the patient.

- The Tcon diluent is provided in an 50 mL infusion bag with a tan label specifying “Step 3b of Administration” (NDC 85866-127-01).
- Store the Tcon diluent at room temperature (18ºC to 25ºC, 64ºF to 77ºF).
- Add the Tcon diluent to the Tcon infusion bag prior to infusion *(see Preparation and Administration (2.2)]*.
- Refrigerate the Tcon diluent at 2°C to 8°C (36°F to 46°F) for 30 minutes prior to use.

17 PATIENT COUNSELING INFORMATION

Discuss the following with the patient receiving TREGZI.

Each TREGZI unit is specific to each patient. The course of therapy for TREGZI is three cell components for infusion, which is provided by the manufacturer as 4 separate infusion bags comprising the HSPCs, Tregs, Tcons, and Tcon diluent. Two infusions, HSPCs and Tregs, will take place on day 0 and one infusion, Tcons, on day +2 to +3 (after the start of HSPC infusion on day 0).

Prior to treatment, advise patients of the following:

Graft Failure
Advise patients that primary graft failure, which may be fatal, can occur *[see Warnings and Precautions (5.1)]*.

Graft-Versus-Host Disease
Treat patients with a single agent calcineurin inhibitor as prophylaxis to decrease the risk of GVHD. Monitor for signs and symptoms of GVHD, and treat if GVHD develops. Report immediately any signs and symptoms suggestive of GVHD, including rash, joint pain, diarrhea, or yellowing of the eyes *[see Warnings and Precautions (5.2)].*

Infusion Reactions
Report immediately any signs and symptoms of Infusion reactions that occur within 24 hours of infusion of TREGZI including fever, chills, flushing, fatigue, shortness of breath, and dizziness/lightheadedness *[see Warnings and Precautions (5.3)]*.

Secondary Malignancies and Malignancies of Donor Origin
Advise patients of the need to contact Orca Bio at 1-877-411-6722 if they are diagnosed with a secondary malignancy or malignancies of donor origin after treatment with TREGZI *[see Warnings and Precautions (5.4)*.

Transmission of Infectious Agents
Advise patients of the risk of transmission of infectious disease *[see Warnings and Precautions (5.5)]*.

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